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SATURDAY JUNE 4 1955

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 4 1955

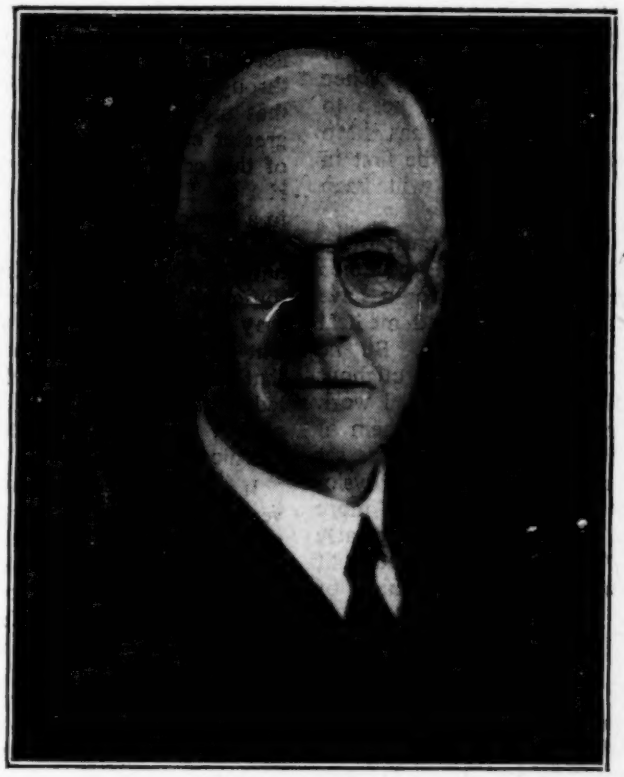
SIR HENRY DALE'S CONTRIBUTION TO PHYSIOLOGY*

BY

LORD ADRIAN, O.M., M.D., F.R.C.P., P.R.S.

Master of Trinity College, Cambridge

There is no one who could write adequately about the whole field of Sir Henry Dale's scientific work, but no one can write about any part of it without feeling that in this case our conventional labels and signposts are a mistake. Certainly he began in the early years of this century with work which would then have ranked as physiology, and he is now regarded by physiologists in every part of the world with the affectionate veneration we reserve for our greatest masters. But his first researches could be claimed now by the anatomists, his major contributions have enriched the fields of pharmacology and therapeutics, and, as head of the National Institute for Medical Research and President of the Royal Society, he has helped to guide the whole course of scientific work in Great Britain.



Sir Henry Dale, O.M.
Sir Henry Dale is 80 on Thursday, June 9.

Labels, in fact, can only tend to obscure what all of us would wish to emphasize, that he has always been the leader who decides where the advance should go and never the subordinate commander who must keep to one sector of the field.

No one could have led as Dale has done if his knowledge of the field had been limited to any one sector. It is true that in the early years of the century, when he began his career in the Wellcome Research Laboratories, the field was a great deal smaller than it is to-day. Biochemistry had scarcely begun, no one measured H-ion concentrations, the hormones were few, and the vitamins had still to arrive. At that time Dale's grasp of the whole range of physiology and of the sciences which could assist it seemed remarkable enough. He could meet pharmacologists, organic chemists, and clinicians on their own ground; he could use their methods as well as speak their language, and could see the bearing of a discovery in one department on the advance of another. But the marvel has been that he can still do so in spite of all the expansion of medical science in this half-century, the entry of biochemistry and physical chemistry, the multiplication of hormones and vitamins and enzymes, and the proliferation of technical terms and methods of every sort. The great triumphs of chemotherapy have been in the field which he knows best, but it is difficult to think of any in which he cannot still hold his own.

Clarity of Ideas

Part of the secret must lie in the clarity of ideas which has always made it a pleasure to read his papers. The volumes of the *Journal of Physiology* in the years before the first war contain many classics, for those were the days when physiology could claim an undisputed leadership; there was also Langley's stern editing to make every writer keep to the point. Dale's papers then were among those which every student could read and remember without any thought of the examinations ahead. They might deal with subjects of forbidding unfamiliarity—β-iminazolylethylamine, for instance—but as soon as one began to read them one could see why Dale thought the subject important, and before one finished it had become evident that he had made it so. He would use the standard techniques of the pharmacologist, the kymographic tracing of blood pressure and respiration and volume change: the records he published left no doubt that his experimental skill was of a very high order, but he avoided unnecessary

*The first of four invited contributions to celebrate the eightieth birthday of Sir Henry Dale on June 9.

The photograph is supplied by Walter Stoneman.

complications and unusual apparatus. There was no need to change the technique so long as it could give decisive answers, and they were decisive because the right questions were asked. In fact, he has been ready to adopt whatever new method would be more effective; but for Dale the technique has always seemed to follow the problem and rarely to suggest it.

Assembling of Evidence

This may do less than justice to the strategy which has led to so many advances. An attack cannot be planned without regard to the arms which can be employed, and Dale has always known where to find them and what to expect from them. His many collaborators and pupils have never found him set in his ways; it is rather that he can develop his theme with such knowledge and authority that in the completed account of an investigation we follow the argument and rarely stop to think of all the difficulties which must have been surmounted in assembling the evidence for it. Yet no one can have seen Dale at work in the laboratory or listened to his communications to the Physiological Society without realizing that it is the evidence which is all-important. Dale has never let his theories take charge: often enough his evidence has led to elaborate theorizing by others—about the role of histamine for instance, or about humoral transmitters in the nerve fibre. When such new horizons are opened it is hard to keep to the solid and familiar ground, but Dale has been more concerned to apply the brake than to be first in the gold rush. The gold he has found will keep its value.

Those who have listened to his lectures must often have been surprised to learn that he has never occupied a professorial chair at a university. He would have shone in teaching as he has in research, and medical education would have profited by his wisdom. But he has taught the whole body of physiologists throughout his career, through the medium of his published work and even more by his personal contact with them at congresses and symposia. For many years he has set the example at the International Congresses of Physiology by showing the rank and file how much more interesting a communication can be when it is clearly presented and illustrated. All of us are agreed that the kymographic records which bear the hall-mark of the National Institute for Medical Research have set a standard which few laboratories can hope to reach.

Such virtues are no doubt of minor account in comparison with Dale's specific achievements in the field of scientific investigation, but his effect on the development of medical science generally has been of major importance. Though he could not serve on the Medical Research Council when he was Director of the National Institute, his ideas have played a large part in the policy of the Council, and his direction of the Institute has led to many developments in fields remote from physiology and pharmacology.

To have remained as fertile in his own researches as Dale has done, as accessible and as encouraging to his juniors, and yet to have made his Institute famous for the variety as well as the standard of its performance is an index of talents and personal qualities which can only arouse our admiration. We cannot feel envy at the power to have accomplished so much; it is too far beyond our reach.

SALUTE TO HENRY HALLETT DALE

BY

OTTO LOEWI, M.D.
Foreign Member of the Royal Society

Sir Henry Dale's eightieth birthday is a welcome occasion for reflections on what science in general and scientists themselves owe to him. Such retrospection is especially gratifying to one who has had the good luck to enjoy Henry Dale's friendship for more than half a century. We met for the first time in 1903, in the small and poorly equipped, yet extremely creative and dynamic laboratory of Ernest Starling. Our interests and aspirations had much in common, and before long a close mutual relationship developed, from which emerged our lifelong friendship. This was deepened when, as time went on, our main interest and work coincided in the field of the chemical transmission of nervous impulses. That such a mechanism existed had been seriously considered first by Elliott (1904) and then by Dale (1914), because of the correspondence they had noted between the effects produced by adrenaline or acetylcholine and those due to the activities of sympathetic or parasympathetic nerves respectively. Later the chemical transmission of impulses from post-ganglionic nerves was established, and then Dale demonstrated, through ingenious planning, methods, and experiments, that the chemical transmission holds good to a much greater extent than I had realized. No better evidence of this can be offered than a quotation from a certain Harvey Lecture (1933): "I personally do not believe in a humoral mechanism in the case of striated muscle." Within the next year Dale demonstrated the chemical nature of transmission from spinal nerves to striated muscles. It was a discovery that made me happy, which may seem strange in view of the sentence just quoted. But it was not strange at all, for the fact stood forth that physiology owed and still owes to Dale the knowledge that the transmission of impulses from *all* peripheral, efferent nerves to their effector organs is of chemical nature.

It is fascinating to follow Dale's development from the very beginning. He was introduced to experimental medicine by some of the great physiologists of those days: Gaskell, Langley, Anderson, Starling, and Bayliss. At the age of 29 he accepted a post as independent research worker in the Wellcome Physiological Research Laboratories. He has since said: "I was attracted to the offer . . . by an instinctive feeling that it would be a good thing for me, at that stage, to be obliged to stand scientifically on my own feet, to find my own problems, to plan my own experimental attack upon them, to learn and devise methods for myself and to make my own mistakes." Dale's continual development ever since has fully justified the early confidence he had in himself. His scientific achievements, here dealt with in tributes from Lord Adrian and Professor Burn, were of such distinction that soon he became a leader in the fields of pharmacology and physiology and attracted a great number of ardent young associates from many lands. Endowed with imagination, strengthened by self-criticism, and urged on by a contagious enthusiasm and intellectual curiosity, he probed into the very roots of his problems and in doing so became an inspiring educator. He familiarized his students not only with facts, methods, and the art of observing and experimenting, but with ways of scientific thinking and

with the principles applicable to any field of experimental science. And more than all this, Dale became and has remained a scientific father and personal friend to his pupils. Small wonder that every single one of them cherishes a deep, unfaltering devotion to him.

In time the realm of Dale's interests expanded so widely that he became master of the essential problems in nearly every branch of experimental medicine. It became almost a routine for other men of wide scientific knowledge to turn to him for advice or to call upon him—again and again from across the Atlantic—to be the chief speaker at the dedication of research institutes. Hardly anyone else would have dealt with the possibilities of these institutes from so many angles or have so clearly indicated the direction research should take in the future. By such deeds Dale has shown himself to be a pre-eminent elder statesman in science.

For years Dale has been besought to deliver speeches on general themes and to commemorate famous men or anniversaries and to dignify special occasions. By consenting to the publication of a selection of such lectures and addresses in a book called *An Autumn Gleaning*, Dale has given us opportunity to broaden our knowledge of his thought and personality. He is as generous in appreciation of the achievements of others as he is modest about his own. In the introduction to the book just mentioned, he suggests that it may be "a late aftermath of weeds." I agree with the reviewer (Hugh Taylor, *American Scientist*, Vol. 43, p. 36, April, 1955) who calls the book "a golden harvest."

Dale's training at Trinity, one of the foremost humanistic colleges, may in part be responsible for his leaning to the historical aspects of science. He follows up the growth of ideas through the centuries and sees scientific developments in their proper setting. Over and beyond his education he possesses the capacity to grasp what is essential. His flair for the essential in any matter is generally recognized. English friends have related to me more than once that, whenever a scientific discussion becomes entangled, everybody eagerly waits for Dale to rescue it; he always makes the point.

Another characteristic of Dale's is his unusual talent to express the wealth of his thoughts by means of deeply penetrating words. More than that he has an artistic mode of formulation, which should serve the younger generation as a prototype of simplicity, lucidity, and beauty.

I finally desire to emphasize—have tried indeed to do it all along—that Dale's intellectual and aesthetic culture are attended by a strong ethical sense. He has a deep feeling of moral obligation. It shines through everything he writes or speaks. He has a genuine eagerness for any good cause.

To do justice to Dale's personality as a whole would require a big volume. In a short essay like this, only a few of his innumerable facets can be singled out.

The achievements of creative men in science, art, and music originate almost entirely from their aspiration to make the best possible use of their natural endowments. Doing so, they are happy and they do not claim gratitude. Their fellow men are grateful to them, in part because they benefit by their achievements, but for a larger reason as well, because these achievements testify to the heights that can be reached by mankind. Contemplating their deeds, we feel pride, courage, and optimism. On Henry Dale's eightieth birthday I feel joy in saying this to him:

Happy birthday, dear old friend.

SIR HENRY DALE'S CONTRIBUTION TO THERAPEUTICS

BY

J. H. BURN, M.D., F.R.S.

Professor of Pharmacology, University of Oxford

In considering Sir Henry Dale's contributions to therapeutics it is right to mention first his discovery of the action of posterior lobe pituitary extract on the uterus. Though he published no paper dealing specifically with the action of this extract until 1909, there is a record of the stimulant action on the uterus of the cat in his paper on "The Action of Ergot," which appeared in the *Journal of Physiology* in 1906. He pointed out the significance of this effect, since he had shown that the uterus of the cat in the non-pregnant state, unlike that of many other animals, was caused to relax by sympathetic stimulation and by the action of sympathomimetic amines.

Dale's main interest until the end of the first world war was in problems which were at first sight academic; his work on the action of histamine on the capillaries, however, had a great impact on clinical thought. It is hard to remember that up to 1918 the current view was that of Tigerstedt, according to which the capillaries lacked the power to contract and were purely passive structures. Dale and Richards in 1918 were the first to demonstrate that the vasodilator action of histamine seen in the body was due to capillary dilatation, and that a state of capillary constriction could be maintained under certain conditions in a perfused limb. This indicated that the capillaries behaved as though they had a tone of their own. Krogh's work, based on the direct observation of capillary changes and published only a few months later, confirmed and amplified the conception of independent capillary activity in great detail.

While the evidence of Dale and Richards and of Krogh was of interest mainly to physiologists, the work of Dale and Laidlaw on histamine shock brought the importance of capillary dilatation and of capillary permeability to the minds of physicians, surgeons, and pathologists alike. Dale and Laidlaw demonstrated that the injection of histamine into the cat anaesthetized with ether caused a profound and irreversible fall of blood pressure due to stagnation of blood in the widely dilated capillaries of the intestine, and that the blood in the main vessels became concentrated by loss of fluid through the capillary walls.

An interesting observation which is still not fully explained appeared in the first paper of the first volume of the *British Journal of Experimental Pathology*. Dale showed that when a cat was anaesthetized with ether or chloroform for some time, and then without operation allowed to recover, it remained for many hours highly sensitive to the effect of injected histamine. Collapse was caused by an amount of histamine one-tenth of that which was without effect on the cat before it received the anaesthetic.

Biological Standardization

The most important contributions to therapeutics were, no doubt, those which came under the heading of biological standardization. The importance of accurate dosage of drugs was always recognized by those who compiled the various pharmacopoeias, but its full gravity was appreciated only when the number of potent remedies underwent rapid

expansion. The appearance of agents the purity and potency of which could not be determined by chemical means gave rise to special problems, for it was not known how to measure these agents with any accuracy. For the antitoxic sera this did not matter so much. Provided that a patient was given not less than a certain dose of diphtheria antitoxin, no harm was done if he received more, and the doctor was satisfied if the manufacturer could assure him a potency which might be greater than the strength stated on the label but was definitely not less.

When the National Institute for Medical Research was established in Hampstead in 1920 there were two problems urgently needing attention. The one was the provision of a standard for the posterior lobe extract of the pituitary body, which varied widely in potency as made by different firms. A method for comparing the potency of two extracts had been described by Dale and Laidlaw in 1912, but there was no agreement between manufacturers about the strength of the extract which should be made commercially available to medical men. After its effect on the parturient uterus was discovered some doctors used it to accelerate the course of labour, and records appeared in the literature from 1910 to 1920 of patients in whom the injection of posterior lobe extract produced rupture of the uterus. In 1920 Dale therefore arranged an investigation, which established that of the extracts available in Britain the strongest was no less than 80 times the potency of the weakest. This meant that a doctor who used the product made by one firm at one time and the product made by another firm at another time might observe a completely different response on the two occasions. Since uniformity could result only when a common standard of reference was available, Dale investigated standards which had been proposed in the United States, showed that they were unsatisfactory because they were not prepared from the posterior lobe, and he suggested in their place a fresh extract of posterior lobe obtained by following a particular procedure. Actually this standard preparation was superseded in 1925 by the acetone-dried powder prepared in the laboratory of Carl Voegtlin, which was more suited not only to national but also to international use. The work, however, achieved a uniformity of potency in Britain from 1922 onwards.

The second problem which demanded attention at that time was presented by the manufacture of neoarsphenamine. German supplies ceased in 1914, and during the first world war the manufacture in Britain was controlled only by a test to ensure that the preparations administered to patients were not unduly toxic. By 1920 there were numerous reports that British neoarsphenamine was much less efficient in therapy than the original German product had been. Dale therefore arranged for tests for potency to be applied as well as for tests for toxicity, the tests for potency being made on mice infected with trypanosomes according to a method described by Voegtlin and Homer Smith. The results supported the clinical opinions and indicated that some samples of British neoarsphenamine were very weak. Not all manufacturers, however, were at that time willing to accept this evidence, and they protested that tests on trypanosomes in mice were not relevant to the cure of syphilis in man. Dale therefore arranged with Dr. C. F. White for a trial of a series of neoarsphenamine samples on men with a primary syphilitic lesion, in order to compare the results so obtained with the results in mice. The comparison provided a complete vindication of the mouse test, and from that time forward all samples of neoarsphenamine made in Britain were examined not only for toxicity but also for therapeutic action. There can be no doubt that Dale's effort in this matter, as in the matter of pituitary (posterior lobe) extract, was a contribution to therapeutics in Britain of very great importance.

The Introduction of Insulin

When Banting and Best announced the discovery of insulin and Macleod and Collip were assisting them to devise a method of preparing solutions for therapeutic use, Dale, with H. W. Dudley as his companion, visited Toronto to learn at first hand of the progress of the work. This visit and the work which followed it enabled insulin to be made available in Britain in the shortest possible time as an agent which from the first was of nearly uniform potency.

The situation was full of dangers. The manufacture of a product like insulin was new to pharmaceutical firms in every country, and it seemed too great an adventure for any single firm in Britain. It involved the preparation of an unstable substance in sufficiently purified form for subcutaneous injection, from a tissue rich in an enzyme which could destroy the insulin, and full of other material. The preparation of insulin had defeated many who had attempted it on a small scale. What was now needed was a large-scale process which could be relied upon to produce insulin with regularity and at reasonable cost. This had to be accomplished with little guidance from previous experience of other tissues. For various reasons Dale sought to persuade the manufacturers who were interested to combine their resources, and it was as a result that the two firms Allen and Hanburys and British Drug Houses united to produce the AB brand. Much work was carried out by Dudley at the National Institute which enabled him to obtain insulin as a picrate, and in this way assistance was given in devising a commercial process. Frequent consultation between Dale, Dudley, and F. H. Carr greatly facilitated large-scale production.

Standardization of Insulin

Still more important, however, was the solution of the problem of standardization, which from the first constituted a serious obstacle to progress in purification. It was studied intensively under Dale's direction. The Toronto workers from the first attempted to measure insulin in terms of a rabbit unit, the definition of which was continually modified in the attempt to make such a unit satisfactory. Difficulty arose from the fact that the injection of the same amount of insulin into different rabbits, even when these were of the same sex and of similar weight, caused a fall of blood sugar which differed in magnitude in different animals. The measurement of the hypoglycaemia in different rabbits took considerable time, and for many months it was not obvious how the variation in the response of different animals could be overcome.

Dale's own view from the first was that the method of standardization could not succeed if it was to depend on a rabbit unit, and that it was essential that the method should be comparative, each preparation of insulin being tested in comparison with a standard preparation to determine the difference between them. This was the basis of Ehrlich's method of standardizing diphtheria antitoxin. Using this as the guiding principle, H. P. Marks, working under Dale's direction, finally arrived at an expression of the hypoglycaemic effect on a series of rabbits in terms of the mean effect in the group. This constituted an important advance which had far-reaching consequences. When a given dose of one preparation was injected into several rabbits the hypoglycaemic reaction of each rabbit differed, as has been pointed out. At that time the question seemed to be which of the different responses was to be regarded as the correct one. A revolution of thinking was required before it was realized that all the responses must be taken into account, and that the correct response was the mean of these very varying responses. Once this had been grasped, it was possible to determine a "dose effect" curve for insulin; that is to say, to determine for each of a series of doses of insulin the mean hypoglycaemic response in several animals.

At this stage a firm basis for insulin standardization had been laid down; it was carried out as a comparison of an unknown sample with a preparation specially kept for use as a standard, so that the potency of the unknown sample could be expressed in terms of the standard. The unknown might be four-fifths of the standard, or it might be one and a half times the standard; the number of units the unknown contained was then determined by the number of units

arbitrarily given to a certain weight of the standard. If it was decided to say that the standard contained 8 units in 1 mg., then it followed that if the unknown was four-fifths of the standard the unknown must contain 6.4 units per mg.

International Standardization

This procedure to-day may seem simple and obvious, but in 1923 and 1924 it was entirely new for a substance such as insulin. The success achieved had a very wide influence on the biological standardization of many other substances. Moreover, it came at a time when the establishment of international standards had been under consideration and provided a compelling reason for international agreement. At the International Physiological Congress in Edinburgh in 1923, Dale, Magnus, and others had considered the question of having standard preparations of various kinds, Magnus being specially concerned with a standard preparation of digitalis. As an outcome the Health Organization of the League of Nations arranged a conference in Geneva in 1925, of which Dale was the chairman. At that meeting international standards were agreed upon by the representatives of several countries for insulin, pituitary (posterior lobe) extract, neoarsphenamine and sulpharsphenamine, and for digitalis. This was a great achievement which was based on a careful organization of experimental work in different countries beforehand, and led to close and friendly relations between all the workers concerned. It meant, for example, in the case of insulin that a uniform system of measuring its potency was adopted throughout the world within four years of its discovery. Had Dale not succeeded in persuading the other members to adopt the comparative method of standardization, the meaning of "one unit of insulin" might well have remained obscure and the potency of different samples have shown wide variation for many years.

So successful was the Geneva Conference of 1925 that later conferences in 1928, 1934, 1935, and 1938 extended the list of substances for which international standards were provided almost as a matter of course. Since the second world war the work has continued under the World Health Organization, and the number of international standard preparations has reached fifty, with another fifty under consideration. How great a contribution this has been to therapeutics throughout the world it is quite impossible to indicate or measure. It is very largely due to Dale's skilful persuasion that instead of confusion there is order and co-operation in a field where national prejudices are sometimes just as capable of preventing agreement as in politics generally.

To conclude this account without reference to the changes in the treatment of myasthenia gravis resulting from Dale's work on skeletal muscle would be wrong. Papers by Dale and Gasser in 1925 and by Dale and Gaddum in 1930 pointed the way to the paper by Dale, Feldberg, and Vogt in 1936. The results described in the last paper stimulated Walker to use physostigmine in myasthenia and later neostigmine. Thereafter the symptoms of myasthenia gravis were for the most part brought under control.

"It is so easy to get the impression, from the popular acclaim which greets its real or imagined achievements, that the life of the research worker must be passed at a level of emotional tension rather like that of a gambler. In past years I have had more than one young man come asking for an opportunity to do whole-time research, and to be paid for doing it, with little to show in the way of credentials, beyond a dislike for the idea of teaching or practice, and a feeling that research must, by comparison, be full of excitement and fun. I did my best to correct that impression. The research worker, if he is successful, may indeed have his moments of discovery and seemingly sudden revelation, from which he may experience more than a momentary exhilaration; but, in spite of what popular report may suggest, such moments do not come merely by fortunate accident."—From *Autumn Gleanings*, p. 139, by Sir Henry Dale.

SIR HENRY DALE: HIS INFLUENCE ON SCIENCE

BY

HERBERT S. GASSER, M.D.

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At the International Congress of Physiology in Boston in 1929 it was easy to arrange a special luncheon in honour of Sir Henry Dale by those whom, at some time previously, he had graciously received as collaborators in his laboratory. The occasion was symbolic of the loyalty and affection of the group as a whole. Those present were holders, or were to be holders, of responsible positions in physiology, pharmacology, biochemistry, and internal medicine. There illustrated was the area of his influence but not its depth. To find an expression for the latter one has to range far from the favoured few who have been with him in his laboratory, and then reflect upon what measuring device can be invoked. In current usage, the adjectives sympathomimetic, cholinergic, and adrenergic enter into descriptions with the readiness of older examples of their kind, as vasoconstrictor or vasodilator. Out in the common domain their influence goes on, though their origin may be forgotten.

Sir Henry's first paper affords us a starting-point. Typical of first papers, its subject matter was probably assigned to him by his professor. It is not one of the sources of the great stream that would develop later and in times of flood overflow its banks to add fertility to the adjoining fields; but it presaged the kind of careful work that makes possible the development of each innovation upon a solid foundation of what has gone before. A half-century later it was to become of great use to me. Also, it supplies us with a date, 1900.

A few years before, the action of an extract of the suprarenal gland had been discovered. It was just becoming associated with the sympathetic nervous system, and the structure of its active principle was still unknown. Acetylcholine had long been in the chemical catalogue, with its pharmacodynamic potency quite unsuspected; and histamine was not yet even a chemical curiosity. Such was the background of the sector of the evolution in the physiological sciences in which Sir Henry Dale's influence was destined to be greatest.

Pure and applied science—why extol one above the other? Where, indeed, is the division? There is but one science: that which, by whichever of its methods, leads to verifiable facts and what can be done with them. For the youthful Dale the course of the main stream was long to follow the saga of ergot. Freedom he had. And it was from the part of his researches that would be called "pure" that the irradiation took place out into the world of physiology and pharmacology, long before the advent of any proper understanding of ergot as a therapeutic agent.

Out of the saga of ergot, as told in the previous papers, now omitting all reference to chronology or collaborators, there can be brought into focus two great sets of contributions: the delineation of the sympathomimetic amines and the description of the actions of the quaternary ammonium bases. Through the whole there had to be carried the theme of adrenaline, which

not long since had been announced. In spite of his early clarifying discovery of the ergotoxin reversal, and in spite of other useful contributions to the mode of its action, again and again he was forced to point out discrepancies in the interpretation of the various experiments.

So fundamental were these developments to an understanding of the control of the circulation, and later to ideas about the nervous system, that each one as it appeared sent its reverberations throughout the laboratories of the world in which these subjects were of interest. To follow them would require a recapitulation of the history of a chapter of the physiological sciences over a half century. But, impossible as is the tracing of irradiation of influence in brief statement, it is still possible to give some hint of how it operated, in an illustration pertaining to the regulation of the vascular system.

Ramifications from Isolation of Histamine

The isolation of histamine and the description of its action, in 1910, may be taken as the point of departure. Here it is convenient also to mention the adduction, seventeen years later, of the proof that histamine is a normal constituent of the body; whereby the growing suspicion that the substance has a physiological significance was confirmed. It was partly the destiny of the analysis of the vasodilator action of histamine to follow a course parallel to that of the vasodilator action of adrenaline. The way of the latter had its rough spots. Annoying differences between the actions of the sympathetic nerves and adrenaline kept obtruding themselves; and the problem of what maintains the vascular tone essential for relaxation by either substance kept resisting a satisfactory solution. Many years were to pass, then at last new light from several of the laboratories of the world: noradrenaline and 5-hydroxytryptamine, each in its way to remove some of the shadows.

In the early experimentation on histamine there occurred a brilliant example of a chance observation appearing before a "prepared mind." Diverted for a time, as the result of a fortunate accident, toward the interpretation of anaphylaxis, Dale in a fundamental contribution not only pointed out the strategy for future work but also supplied an important part of the tactics. The significance of antigen meeting antibody in the organs still stands. The "Dale" bath is still in use. Here is an influence with a history of its own extending throughout a specialty. It might be characterized as pertaining to an offshoot from what I have called the main stream, were it not for the fact that histamine, which opened the front door, again crept in at the back. Its reentrance, however, is connected with a larger subject: tissue injury.

During the first world war physiologists turned their attention to wound shock. It is not for me to recount Dale's comparisons of histamine shock and wound shock, but to turn to the aftermath. At the time facts were missing, needed for interpretations. A forced conclusion was that there was no justification for assuming that histamine is the only cell constituent which injury liberates. In the subsequent history, with the entrance of heparin on to the scene, the incoagulability of the blood was accounted for. With the second world war came the description of "precapillary sphincters" susceptible to influence by products of tissue injury. More recently has come the claim that ferratin has such an action.

Through work in widely separated laboratories attention has been directed to mast cells. They first came into prominence when heparin was associated with their granules. Their prominence became enhanced when histamine was found in the same location. At last a source of bound histamine in the tissues, long postulated, had been found. Since these cells are widely distributed along the course of the smaller blood vessels, they are well placed for participation in vascular reactions. Consequently, new perspectives of interpretation are opening up—as, for example, in relation to the triple reaction of the human skin. Histamine research has come to full flower.

In 1910 it would have been impossible for anyone to foresee the number and extent of the ramifications from the description of the action of histamine. Along each of the branches there has been a succession of investigators. Now, the groups situated at the growing ends of the branches, as they look back over their specialized histories, find a meeting-place at a common point.

One, indeed, wonders what some future commentator will have to say in addition; especially in view of the rapidly changing frontier in pharmacology. As a science, pharmacology itself has matured. From its origin, wherein it was devoted to experimental testing of the validity of its inherited accumulation of empirical lore, it has evolved to a stage at which its investigations can be guided by working hypotheses, comprehensive in their scope. Substances identified in the body have contributed largely to the therapeutic armamentarium. Bodies of unrelated facts have been brought together into an understandable whole. Some of the most powerful pharmacodynamic agents, like acetylcholine and histamine, have turned out to be highly important in the operation of physiological mechanisms, while chemical prowess has been able to prepare molecules with actions imitative or antagonistic. For other powerful agents, to the action of which no clue has yet been discovered, patterns of thought have come into existence to point out the way in which solutions are most probably to be found.

Significance of Acetylcholine

In a search for an analogy for the wave of curiosity that swept through the minds of physiologists in the early 'twenties, after Professor Otto Loewi published his famous papers, there rises into view recollections of what happened more than a century earlier. Just as in the earlier time everyone felt impelled to experiment with the Galvani fork, so in the later time there was a strong desire to see personally the experiment on the frog heart. For an understanding of the revolution that had been launched, familiarity with Dale's papers on the amines and quaternary bases had laid a solid foundation. Now his differentiation of the nicotine-like from the muscarine-like action of acetylcholine would mount into a position of enormous importance.

Much as he had done in contributing to the physiological world the basis for a receptive understanding of the rapid surge of events, it was Dale himself who was in the best position to make effective use of those contributions. How he influenced the course of events can henceforth be derived directly, step by step, from the description of the successive accomplishments by himself and his colleagues: finding acetylcholine as a normal constituent of the body, its liberation during synaptic transmission through sympathetic ganglia, and its liberation at myoneural junctions. As experimentation spread to a world-wide scale, sober expressions of doubt appeared on the one hand, and over-enthusiastic extrapolations on the other. These he met or modulated by powerful arguments in a succession of lectures, both at home and abroad. Who can say where we now stand in the history of chemical transmission? Certainly the subject has not evolved to a point whereby it can explain all transmission. If I am not misinterpreting a recent statement by Sir Henry, it amounts to a cautious intimation that there may be transmitters as yet unknown. Such an intimation could well be taken seriously.

International Recognition

As, year by year, Sir Henry's contributions became more and more interwoven in the general fabric of his science, international recognition of the originator of these contributions grew in proportion, expressed by the long list of his

honorary memberships in foreign societies with particular designations and national academies and societies of science and learning devoted to broader purposes. Thus he became an outstanding representative of that ideal of science which knows no frontiers, in an age when political disturbances engendered upheavals of a magnitude without previous parallel. When the storm abated it was apparent to all that not even science had emerged unscathed. To return to its proper position in society it must pass through a healing process. By virtue of his position Sir Henry was favourably situated to come forward effectively on behalf of the restoration; and he did.

The particular occasion to which I would refer, though it is not the only one, is that of his Pilgrim Trust Lecture delivered before the National Academy of Sciences at a joint meeting with the American Philosophical Society, held in Philadelphia in 1946. On his chosen topic, "The Freedom of Science," he talked calmly and objectively; but through his reasoned words there could not fail to shine light from incandescent feeling behind them. It is always unfair to quote out of context even the choicest passages of a discourse of this sort. For those not among the favoured listeners the whole must be read in order to get its import.

It is the right and duty of every scientist boldly to examine nature without restriction of purpose or fear of outcome, and to communicate the findings openly in order that the aggregate can be tempered under the impact of general criticism. No surer way has ever been invented for determining the laws that cannot be transgressed with impunity in the course of human behaviour. If science has been misused, the misuse is without uniqueness among man's activities; and the way to salvation is not imminent through a study of cause and effect for science alone. True it is that the prime instinct of all living things is for survival. Although at times a retreat may be justifiable for the protection of both civilization and science, in the long run, to prevent undue curtailment of the freedom of science in the name of survival, relentless vigilance is needed.

PULMONARY OEDEMA*

BY

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Pulmonary congestion and oedema are the most common manifestations of left ventricular failure, and may range in severity from the basal rales of chronic congestive failure to acute pulmonary oedema and attacks of cardiac asthma. More recently an intermediate group of cases with subacute pulmonary oedema has been recognized, caused by uraemia, malignant hypertension, polyarteritis nodosa, and the "rheumatic lung." Although the symptoms, signs, and radiological changes of pulmonary oedema are well recognized, its pathogenesis in heart failure is still uncertain, and until recently there was little information on the circulatory changes in the lungs in man. The occurrence of attacks of pulmonary oedema during the course of cardiac catheterization has enabled these changes to be studied, and the altered distensibility of the congested and oedematous lung has been investigated. These results have thrown new light on the problem of cardiac dyspnoea, and it is my purpose to review this recent work and to attempt to correlate it with the various manifestations of pulmonary oedema.

The subject of pulmonary oedema has been extensively studied by experimental physiologists, who have shown that in animals pulmonary oedema may be produced by increased pressure in the pulmonary capillaries, by increased capillary permeability caused by anoxia, phosgene, and certain other chemicals, notably the thiourea compounds, or by neurogenic vasodilatation of the capillaries with resulting increased permeability, the stimulus arising either from direct excitation of nervous centres, as in head injuries, or reflexly from stimuli arising in the heart or large vessels. The type of pulmonary oedema produced experimentally in a normal animal, however, bears little resemblance to the clinical attack of acute pulmonary oedema which occurs in a patient with a long history of chronic pulmonary congestion, and for this reason caution is necessary in applying the results of these animal experiments to man.

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Acute Pulmonary Oedema

I shall use the term "acute pulmonary oedema" to include both cardiac asthma and paroxysmal nocturnal cardiac dyspnoea. These terms merely emphasize particular clinical features of the attacks, but the fundamental mechanism is the same.

Aetiology.—Most cases of acute pulmonary oedema are due to left ventricular failure caused by hypertension, coronary artery disease, or disease of the aortic valve. The group of cases with pulmonary oedema caused by cerebral vascular accidents or fractures of the skull is of particular interest in relation to the pathogenesis of the oedema (Cameron, 1948). In comparison with left ventricular failure, mitral stenosis is an uncommon cause of pulmonary oedema, and the high incidence of this symptom in recently published series of cases of mitral stenosis (Wood, 1954) is due to the recognition of the fact that the most spectacular results of mitral valvotomy are found in this particular group of cases.

Historical.—The clinical features of an attack of acute pulmonary oedema were fully recognized in the early years of the last century, and in 1832 James Hope, who first used the term "cardiac asthma," described the mechanism of the attack, and the circulatory measurements which are reported later are a striking confirmation of at least part of his theory. He wrote that "while the left ventricle was palpitating to disgorge itself, the right, acting in concert with it, deluged the lungs with an inordinate quantity of blood, whence ensued a paroxysm of dyspnoea."

Clinical Features

The clinical manifestations of acute left ventricular failure were fully described by Bedford (1939). Nearly always these attacks occur in patients with a background of chronic pulmonary congestion, as shown by the history of increasing effort dyspnoea and often orthopnoea. A short, dry, frequently repeated cough is usually the earliest symptom and may be associated with a sense

of oppression in the chest. At the height of the attack the most striking feature is intense dyspnoea, often with wheezing, and the increased effort of breathing is shown by the laboured respiration. The chest appears over-distended, and on auscultation a notable feature is the absence of added sounds in the lungs in the very early stages of the attack in spite of the intense dyspnoea.

In short attacks the lung may remain clinically dry throughout or a few rales may appear in the mid-zones or at the bases. In longer-lasting or more severe attacks signs of moisture soon appear and increase until, at the stage when frothy fluid is being coughed up, bubbling rales can be heard all over the chest. In less severe attacks there may be only nocturnal cough and wheezing on lying down, rapidly relieved when the patient sits up. Normal sinus rhythm and pulsus alternans are frequently present. Tachycardia is a constant feature, the rate frequently exceeding 120 a minute. The blood pressure during attacks rises abruptly, particularly in the hypertensive cases, the increase being caused by marked peripheral vasoconstriction as shown by the pallor and coldness of the skin. Cyanosis in the early stages, or in short attacks, is rarely marked, and if present is peripheral in type; during the frothy stage of a severe attack there is increasing cyanosis of central type.

In severe attacks death may occur from asphyxia, or signs of peripheral circulatory failure and shock may appear, cyanosis being replaced by a dusky grey colour of the skin, the blood pressure falls to a low level, and the pulse is rapid and feeble. The breathing now becomes shallow and is no longer laboured, and it is evident that the pulmonary oedema has been decreased by the onset of peripheral circulatory failure.

In mitral stenosis the attacks are sometimes of unusual severity and may fail to respond to the methods of treatment which are usually effective in attacks caused by left ventricular failure, so that an emergency valvotomy may be necessary. More often they are of shorter duration and may be precipitated by emotion, exertion, tachycardia from any cause, or enforced recumbency during cardiac catheterization (Lenègre and Scébat, 1952). During these short attacks dyspnoea is marked and there is often a little frothy blood-tinged sputum.

If acute pulmonary oedema is caused by failure of the left side of the heart there is nearly always a previous history of dyspnoea on effort due to chronic pulmonary congestion, but occasionally it may occur as the first symptom in a previously healthy person as a result of cardiac infarction. The usual pain of infarction may be absent, the patient rapidly becoming dyspnoeic and coughing up large amounts of frothy fluid. These cases should be distinguished from those in which the initial ischaemic pain disappears with the onset of shock and on recovery from shock pass rapidly into acute left ventricular failure with pulmonary oedema. In these patients the blood pressure falls, often abruptly, during the acute phase, and this contrasts with the rise in pressure which is the rule in the attacks due to hypertensive failure. The electrocardiogram will show the typical changes of cardiac infarction, although not infrequently these may not appear until several days after the onset of the attack. An attack of acute breathlessness at night occurring in middle-aged or elderly patients, with no previous dyspnoea and with no history of a recent respiratory infection with bronchospasm, may well be caused by cardiac infarction, and if the blood pressure falls during the stage of intense dyspnoea this diagnosis is even more probable.

The rare cases of an acquired ventricular septal defect due to rupture of a septal infarct are interesting physiologically, as they illustrate the effect of a combination of a sudden increase in pulmonary blood flow due to the left-to-right shunt and damage to the left ventricular muscle in causing pulmonary oedema. In three cases I have seen in which the diagnosis was made during life, acute pulmonary oedema followed rapidly on the rupture of the septum; in two cases there was little response to treatment, and the patients died 7 to 10 days later. The third lived for a year with orthopnoea, recurrent acute pulmonary oedema, and severe right-sided failure. These cases present a striking contrast to those patients who have an acquired intracardiac shunt due to rupture of a sinus of Valsalva aneurysm into the right heart, with a healthy heart muscle, and in whom the sudden increase in pulmonary flow may not cause oedema of the lung. One such patient lived for over a year and died of a carcinoma of the rectum. A second went successfully through a pregnancy four years after the rupture of her aneurysm, and, even with the increased blood volume of pregnancy and the effect of the placental arteriovenous shunt, developed only minimal signs of basal congestion during the later months of pregnancy.

Rupture of an aortic valve cusp sometimes due to bacterial endocarditis may precipitate acute left ventricular failure, and severe pulmonary oedema may cause the death of the patient.

Physiological Factors

The factors responsible for the formation of oedema fluid in the lungs are fundamentally the same as those concerned in the production of oedema elsewhere in the body, and are (1) hydrostatic pressure relationships, (2) osmotic factors, and (3) the permeability of the capillary wall.

By impaction of the end of a cardiac catheter in a small terminal branch of the pulmonary artery it is possible to obtain pressure readings—"the wedge pressure" or "pulmonary capillary venous pressure"—which reflect with reasonable accuracy the pressure changes in the pulmonary veins and left atrium (Epps and Adler, 1953). The mean left atrial pressure measured in this way is usually 5 to 10 mm. Hg, and the true pulmonary capillary pressure cannot be less than this figure. The intrathoracic pressure variations with respiration will affect pressure in the capillaries and interstitial tissue equally, and so will have little effect on the effective filtration pressure in the capillaries, which in the normal lung is in the region of 5 to 10 mm. Hg.

The osmotic pressure of the plasma proteins in the pulmonary capillaries is the same as that elsewhere in the body—that is, 25 to 30 mm. Hg with the normal plasma protein level of 7 g.%. It is probable, however, that the effective osmotic pressure tending to prevent leakage of fluid through the capillary wall is appreciably lower than this. No information is available on the protein content of interstitial fluid and lung lymph in the normal human, but in normal animals there is considerable leakage of protein, which reaches a concentration of 2.5 to 3 g.% in the lung lymph with an osmotic pressure of about 11 mm. Hg (Warren and Drinker, 1942). If, as seems likely, the same happens in man, the effective osmotic pressure will not be more than 20 mm. Hg.

Studies of lymphatic flow in animals show that significant amounts of protein and fluid escape from the vessels into the interstitial tissue of the lung and are removed by the lymphatics. If the permeability of the capillaries is increased, either by anoxia or by capillary toxaemia, a

considerable increase in the amount of fluid escaping occurs and pulmonary oedema results, the oedema fluid having the same protein content as normal lung lymph (Drinker, 1945). The effect of neurogenic factors on the permeability of the capillary membrane has been the subject of much experimental work. Parts of the pulmonary vascular bed are certainly supplied with functionally active vasomotor fibres, and there is evidence, both clinical and experimental, pointing to some influence of the nervous system in the permeability of the lung capillaries (Daly, 1946), but the importance of this factor in human pulmonary oedema is still conjectural.

In the normal person the relatively low filtration pressure and higher osmotic pressure will reduce the transudation of fluid in the lung to a minimum, and any fluid which may escape is efficiently removed by the lymphatics. If, however, the filtration pressure in the pulmonary capillaries exceeds the effective plasma osmotic pressure, or if the permeability of the capillaries is increased in any way, fluid may pass through the capillary wall into the interstitial tissues of the lung. The barrier separating the plasma in the capillaries from the alveolar spaces in the normal lung is extremely thin, about 0.8 μ, composed of the capillary wall, thin interstitial tissue, alveolar lining membrane, and

FIG. 1.—Thickening of alveolar and capillary lining in mitral stenosis. (×700.)

mucin layer (Macklin, 1954); so that if the lymphatic channels, which start in this region, are unable to remove the fluid as fast as it is formed, it can readily escape into the air passages, to produce the frothy fluid of pulmonary oedema.

In mitral stenosis or chronic left ventricular failure transudation of fluid from the capillaries may be hindered by thickening of the basement membrane and the barrier layer may be much thicker, often as much as 15 μ (Fig. 1), due to thickening of the alveolar epithelium and structural changes in the interstitial tissue (Parker and Weiss, 1936), so that, even if there is interstitial oedema, fluid may not be able to pass readily into the air passages, and the lungs may be clinically dry. The absence of structural changes in the lung may be one reason why larger amounts of frothy fluid are frequently coughed up in attacks due to cardiac infarction than in those due to chronic left-sided failure, where intense dyspnoea may dominate the clinical picture of cardiac asthma.

Circulatory Changes During Acute Pulmonary Oedema

Until recently no accurate measurements of the circulatory changes in the lungs during attacks of pulmonary oedema have been possible, although the presence of pulmonary hypertension during the attacks has been inferred from the marked pulsation over the ventricle and pulmonary artery and the loud pulmonary second sound (Bedford, 1939). A number of patients with mitral stenosis have developed acute pulmonary oedema during the course of pre-operative cardiac catheterization, and circulatory measurements have been made during these attacks. They were precipitated by a variety of causes, such as anxiety, prolonged recumbency, or exercise, and were usually short-lasting, but were apparently identical with the spontaneously occurring attacks, with cough, dyspnoea, and expectoration of frothy sputum. From personally observed cases and from reports in the literature (Gorlin *et al.*, 1951; Lenègre and Scébat, 1952; Lenègre *et al.*, 1953) measurements in 23 cases of pulmonary oedema have been collected, and in 6 cases studies before and during the attacks have been made (Fig. 2). Details of a small number of attacks of acute pulmonary oedema occurring in the course of physiological studies on patients with left ventricular failure have also been obtained from the literature.

In attacks due to mitral stenosis (Fig. 2) there is usually a slight to moderate increase in the pulmonary artery pressure before the attacks, and during the attacks the pressure

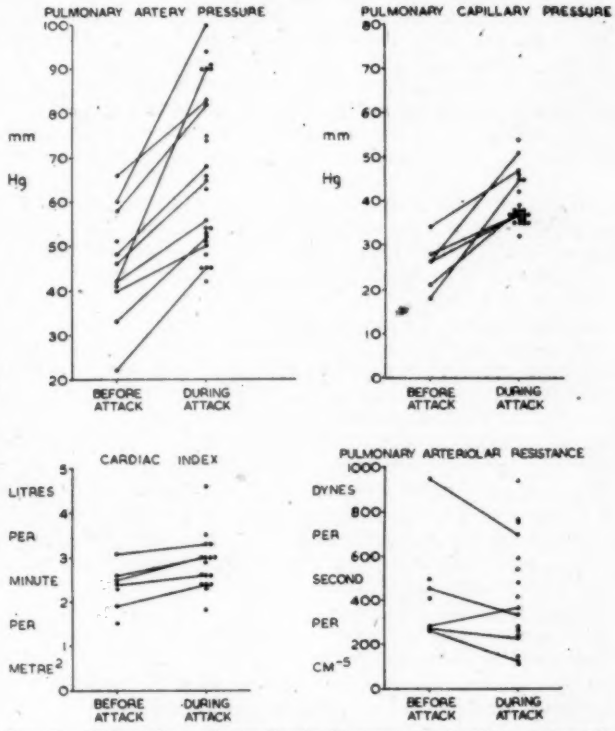

FIG. 2.—Haemodynamic studies in 23 cases of mitral stenosis with acute pulmonary oedema.

rises abruptly. The "pulmonary capillary" pressure before the attack was raised to between 25 and 30 mm. Hg and during the attack rose to a level between 32 and 54 mm. Hg. In 15 of the 23 cases the pressure was between 35 and 38 mm. Hg. The cardiac output before the attack was usually slightly below the average normal of 3 litres per minute per square metre. During the attack a slight rise in output is common, but this figure may be inaccurate because of the obvious difficulties of measuring the factors necessary for its calculation according to the Fick principle during an attack of acute dyspnoea. The pulmonary arteriolar resistance before the attacks shows a slight to moderate increase, and changes in resistance during the attack are variable. No case of acute pulmonary oedema occurred in patients with a very high resistance. The work of the right ventricle was increased in all cases, and its ability to carry out the work without any significant increase in the end-diastolic pressure is in keeping with the clinical observation that marked systemic venous engorgement is unusual during an attack of pulmonary oedema.

Catheter studies on patients during acute pulmonary oedema due to left ventricular failure are infrequent, but in all recorded cases the pattern is the same—that is, an abrupt rise in pulmonary artery and "pulmonary capillary" pressure, the latter in all cases exceeding 30 mm. Hg, and a slight rise or no change in cardiac output. The pulmonary artery/pulmonary capillary pressure gradient is usually unchanged during an attack. The arterial oxygen saturation before the attack was usually reduced—with figures between 84 and 96% saturation. In these short attacks a slight fall in arterial oxygen saturation sometimes occurred, as was to be expected, but it was surprising to find a number of patients with an initially somewhat low saturation who actually increased their arterial oxygen saturation during an attack which caused intense dyspnoea. In severe attacks there is profound arterial anoxia, with levels sometimes as low as 45% saturation.

Mechanism of the Attack

The level of the "pulmonary capillary" pressure in all recorded attacks of pulmonary oedema due to left ventricular failure or mitral stenosis has exceeded the plasma osmotic pressure, often by a considerable margin, and this would seem to be a clear demonstration of the mechanism of the attack. In the cases presented here this margin has been an appreciable one, as the effective plasma osmotic pressure is probably not more than 20 mm. Hg and the "pulmonary capillary" pressure has usually been over 35 mm. Hg. This may not, however, be the sole mechanism, as will be seen if the effects of exercise in patients with mitral stenosis or left ventricular failure are studied. In a group of patients with mitral stenosis, whose disability varied from Grade 1 to Grade 4, and many of whom gave a history of attacks of nocturnal dyspnoea, exercise for three to five minutes in the recumbent position produced changes in cardiac output, pulmonary artery pressure, and pulmonary capillary pressure which are exactly comparable to those recorded during acute pulmonary oedema, and yet in no patient did such an attack occur (Fig. 3). In patients with left ventricular failure, effort produces exactly the same change (Lewis *et al.*, 1953). Many patients tolerated this mild exercise well, and, in spite of a considerable elevation of "pulmonary capillary" pressure, in several cases to over 50 mm. Hg, no acute oedema developed.

There are several possible explanations for this discrepancy. One is that the thickening of the pulmonary capillary wall or alveolar lining described earlier hinders the escape of fluid from the capillaries into the air passages, and that this enables some patients to withstand the high pressures without clinical oedema developing (Araujo and Lukas, 1952). Another is that in acute pulmonary oedema the speed of transudation of fluid from the capillaries is suddenly increased, and in the absence of a significant increase in the rate of blood flow through the lungs this must be due to an increase in capillary permeability. The lung capillaries usually allow some protein to escape, and in acute pulmonary oedema the protein content of the frothy sputum, the lung oedema fluid, and fluid from a hydrothorax, if this is present, contains from 2.5 to 3.5 g. of protein%. The idea that increased capillary permeability is responsible for acute pulmonary oedema has long been favoured by experimental physiologists, but the only factor, excluding drugs and poisons, which is known for certain to produce this effect is anoxia, and in the early stages of the attacks there is no evidence of anoxia. It is in the later stages of the attack that anoxia becomes important, and then it may well augment or perpetuate the clinical attack.

The idea of neurogenic factors altering capillary permeability is still a theoretical one, and many of the experiments which purported to demonstrate such an effect, such as injecting substances into the floor of the fourth ventricle (Cameron and De, 1949), have subsequently been shown to cause an increase of left atrial pressure to a level of over 30 mm. Hg (Sarnoff and Sarnoff, 1952). Clinically, the view that increased capillary permeability causes acute pulmonary oedema has always had many supporters, and this factor is often invoked to account for the occurrence of attacks in sleep or as a result of excitement, emotion, or anxiety. So far as the last factor is concerned, it is common to find that if during cardiac catheterization the patient is apprehensive the pulmonary capillary and pulmonary artery pressures rise, and with reassurance or sedation will fall to much lower levels. The action of morphine or the barbiturates in stopping attacks is commonly explained on the basis that they damp down pulmonary vasomotor reflexes, but the true explanation of the action of morphine may equally well be that it lowers capillary pressure by decreasing anxiety, decreasing the muscular movements which are increasing the venous return to the heart, and decreasing metabolism, which will lower the oxygen needs of the tissues and hence lower the cardiac output.

Factors Responsible in Mitral Stenosis

The factors responsible for this high pulmonary capillary pressure in mitral stenosis have been discussed by Gorlin *et al.* (1951), who showed that in the presence of severe stenosis a high left atrial pressure is necessary to produce a rate of flow through the narrowed valve sufficient to fill the ventricle in diastole and to maintain the cardiac output. In acute pulmonary oedema when the cardiac output is almost unchanged, tachycardia is a constant feature during the attack, and Gorlin *et al.* have shown that even a slight increase in heart rate of 10 to 15 a minute will shorten the diastolic filling period of the left ventricle and render necessary a higher pressure gradient across the mitral valve. Momentary disproportion between the output of the right and left ventricle is a factor which may elevate the pulmonary capillary pressure, but with present techniques this cannot be detected. These changes in pulmonary capillary pressure are brought about by only a slight increase in pulmonary blood volume, owing to the relatively inelastic pulmonary venous and left atrial compartments (Ball *et al.*, 1952). These patients usually have only slight to moderate enlargement of the left atrium, and in patients with massive left atrial enlargement, commonly due to mitral incompetence, large volume changes are possible with relatively little change in pressure and attacks of acute pulmonary oedema are uncommon.

In attacks due to left ventricular failure the high left atrial

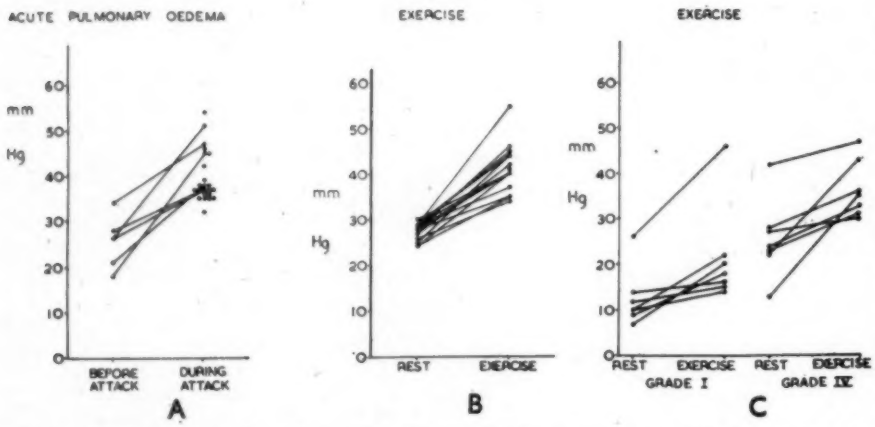

FIG. 3.—"Pulmonary capillary" pressures in acute pulmonary oedema (A) and at rest and on exercise in mitral stenosis (B), and in left ventricular failure (C). (C drawn from data taken from Lewis *et al.*, 1953.)

pressures are probably associated with a high left ventricular filling pressure, which is necessary to maintain the output of the failing left ventricle. The contrast between the performances of the right and left ventricles in pulmonary oedema is striking, the right ventricle carrying out increased work with a normal filling pressure and the left doing so only because of considerable increase of filling pressure.

It has recently been suggested (Burch and Romney, 1954) that active constriction of the pulmonary veins may be partly responsible for the rise in pulmonary capillary pressure—the so-called "pulmonary venous throttle mechanism." In mitral stenosis the pulmonary veins at necropsy are often small and contracted (Holling, 1951), and in life have been shown by tomography often to be smaller than usual (de Bettencourt *et al.*, 1953). There is certainly a plentiful supply of nerve fibres to the pulmonary veins, but there is no proof that pulmonary venous constriction does in fact occur.

The conclusion to be drawn from this haemodynamic study is that acute pulmonary oedema in patients with cardiovascular disease does not occur unless the left atrial and pulmonary capillary pressures exceed by a considerable margin the effective plasma osmotic pressure. The additional factor of increased pulmonary capillary permeability may in some cases be responsible for the sudden outpouring of fluid, which eventually escapes into the air passages. The probable sequence of events is that there is initially acute interstitial oedema of the lung, but that the fluid is removed by the lymphatics and none escapes into the alveoli. This corresponds with the attacks of paroxysmal dyspnoea, during which the absence of moist sounds in the lungs is a striking feature. If transudation persists the lymphatics become unable to deal with the fluid, which then escapes through the barrier layer of alveolar epithelium and mucin to enter the air passage, and a frank attack of acute oedema with frothy sputum results.

The cause of the actual attack of acute pulmonary oedema can in most instances be explained by these haemodynamic changes, which increase pulmonary capillary pressure. Tachycardia, whether caused by emotion, anxiety, exertion, or infection, is responsible for many of the attacks, particularly in mitral stenosis. Attacks occurring during sleep are sometimes caused by the orthopnoeic patient slipping down in the bed and increasing the pulmonary congestion and oedema. Another explanation which has some evidence to support it is that sudden movement while asleep following a period of muscular relaxation may cause a considerable increase in the venous return to the heart. Continuous recordings of heart rates show that even in the healthy individual a transitory increase in the heart rate of 30 to 40 beats a minute may occur during sleep, and if this occurs in a patient with heart failure it may precipitate an attack (Christie, 1938).

Treatment

The recognition of the fact that acute pulmonary oedema does not occur unless there is a considerable increase in pulmonary capillary pressure places on a rational basis most of the methods of treatment which are effective in this condition, as anything which decreases the venous return or lowers the capillary pressure is likely by itself to stop an attack if given before the stage when there is severe anoxia which has increased capillary permeability. Venesection, limb tourniquets, or drugs such as theophylline with ethylenediamine act in this way, the latter also relieving bronchospasm. The ganglion-blocking drugs, such as hexamethonium, which produce peripheral vasodilatation and a fall in systemic pressure, are often remarkably effective in stopping attacks of acute pulmonary oedema, the dyspnoea being relieved soon after the blood pressure has been lowered by slow and cautious intravenous injection of the drug. The method of action of morphine has already been described.

Digitalis would seem to have an obvious place in the treatment of acute pulmonary oedema, as it increases the efficiency and improves the emptying of the failing left ventricle. If given intravenously, for speed of action, it may sometimes have a marked pressor effect; and Bayliss *et al.* (1950) have described three cases of acute left ventricular failure which were caused in this way by digoxin. For this reason it is best given orally, and some additional more rapidly acting drug is necessary during the acute stage of the attack. General anaesthesia in patients with pulmonary oedema, prior to either mitral valvotomy or emergency surgery, often produces a remarkable improvement in the patient's condition and signs of oedema decrease and may disappear. The combination of a good airway, high oxygen content of inhaled air, and muscular relaxation with low venous return is probably responsible for this improvement. The frothy character of the oedema fluid due to its high protein and mucin content has led to the use of antifoaming agents, given by inhalation, in the treatment of acute pulmonary oedema, and good results have been reported (Goldmann and Luisada, 1952).

Direct evidence of the value of lowering the pulmonary capillary pressure is given by the effect of a successful mitral valvotomy in relieving attacks of acute pulmonary oedema. The left atrial pressure is lowered, often to normal figures, immediately after valvotomy (Munnell and Lam, 1951), and the effect of this can be observed at the time of operation, when the congested and oedematous lung becomes dry and the dilated subpleural lymphatics shrink.

Any procedure which reduces chronic pulmonary congestion will diminish the danger of acute pulmonary oedema. Treatment between attacks with digitalis, salt restriction, and the regular use of the mercurial diuretics, with a sedative at night, will often lessen the frequency of attacks, and may stop them altogether.

Subacute Pulmonary Oedema

An unusual type of pulmonary oedema which is subacute in its clinical course is seen in several diseases, all of which are associated with left ventricular strain. It occurs in uraemia, acute nephritis, polyarteritis nodosa, malignant hypertension, and as the "rheumatic" lung in acute rheumatism. The pathological, clinical, and radiological changes are identical in all these diseases with the exception of some cases of polyarteritis. The lungs are solid and rubbery in consistency, particularly in the perihilar region. Histologically there are an early interstitial oedema and an intra-alveolar fibrinous exudate, later infiltration of the exudate with mononuclear cells and fibroblasts, and dilatation of the alveolar ducts, which are lined by a hyaline membrane (Hadfield, 1938; Doniach, 1947).

The fundamental difference between subacute and acute pulmonary oedema is that in the former the exudate clots and is then organized. Clinically there is intense dyspnoea, although the lungs may show no abnormality on clinical examination, and the scarcity of added sounds in the chest is in striking contrast to the extent of the lesion seen radiologically. Episodes of acute pulmonary oedema may be superimposed, often as a terminal event. The scarcity of added sounds in the lungs in this group is explained by the organization of alveolar exudate which has a high fibrin content. Occasionally in polyarteritis nodosa there may be extensive radiological and pathological changes in the lungs, although the patient has no signs or symptoms referable to the chest. In one such case the organizing exudate was almost entirely confined to the interstitial tissue of the lung. The histological and clinical picture of subacute pulmonary oedema suggests that it is due to a combination of altered capillary permeability and left ventricular failure.

Radiology

The radiological features of acute pulmonary oedema have been reviewed by Jackson (1951). The typical appearance consists of dense cloudy opacities spreading outwards from the hilar into the central parts of the lung, obscuring

the lung markings, and leaving the peripheral parts of the lung clear. If the lungs of patients dying with pulmonary oedema are *x*-rayed after removal from the body the opacities are seen to be much more extensive, clouding those parts of the lung which appear translucent in the ordinary film. The rapidity with which these changes disappear, often in less than 24 hours, and the distressed state of the patient account for the difficulty in getting adequate films in acute pulmonary oedema. In subacute pulmonary oedema the opacities are rounded and more definite, corresponding to the rubbery areas which are found at necropsy, and in addition the changes of ordinary acute pulmonary oedema may be superimposed.

Relationship between Pulmonary Oedema and Dyspnoea

Dyspnoea is the chief symptom of left heart failure and is seen in its most extreme form in acute pulmonary oedema, where the intense effort of breathing is obvious. The intensity of respiratory effort or the force exerted on the lungs can be measured in patients made dyspnoeic by exercise by recording changes in intrathoracic pressure, using an oesophageal catheter; and in heart failure this force may be almost as great as in the normal person, although the resultant volume of pulmonary ventilation is much less owing to the increased rigidity of the lung (Marshall *et al.*, 1954). The cause for the increased rigidity at rest is probably the structural changes in the lung previously described, and the further increase in effort is usually ascribed to passive congestion of the lung, although from animal experiments (Hayward and Knott, 1954) it seems probable that pulmonary oedema is a more potent factor than pulmonary congestion in increasing the rigidity of the lung.

The amount of blood in the pulmonary capillaries at any one time is only about 50 to 60 ml. in the normal subject (Roughton, 1945) and the amount of extra blood in them during passive congestion may be small. Kopelman and Lee (1951) measured the intrathoracic blood volume in patients with mitral stenosis and left ventricular failure and showed that, whilst in mitral stenosis it is normal and in left ventricular failure increased, no significant change takes place when recovery from failure occurs. Studies on the effects of exercise (Fig. 3) on patients with heart failure show that even with mild exercise the pulmonary capillary pressure may exceed the effective plasma osmotic pressure, so that interstitial oedema may well be occurring in this early stage in development of failure, but the lymphatics may be able to remove it before it enters the air passages. This is supported by the well-recognized clinical fact that the dyspnoea of early hypertensive heart failure can occur without signs of moisture in the lungs, although the chest *x*-ray film shows an increase in hilar markings, and the mercurial diuretics will cause a diuresis and improve the dyspnoea. The concept that lung oedema is responsible for the altered distensibility of the lungs and cardiac dyspnoea is supported by measurements of lung rigidity before and after mitral valvotomy.

Hayward and Knott (1955) showed that after a successful mitral valvotomy the distensibility of the lung is improved, and that on exercise the lung behaves as does the normal lung, no increase in rigidity occurring. The improvement can be attributed to the fall in left atrial and pulmonary capillary pressure, and these measurements provide one explanation for the marked improvement in dyspnoea which often occurs in spite of no significant change in cardiac output or pulmonary artery pressure or in the result of lung-function studies. Pre- and post-operative chest *x*-ray films in successful cases often show no appreciable difference, and this again suggests that changes in the pulmonary capillaries which are invisible in the chest film are responsible for the improvements in effort tolerance.

In acute pulmonary oedema the rigidity of the lung may be enormously increased and the intense respiratory effort may produce only a small amount of lung ventilation. Thus in one patient the intrathoracic pressure swing was 30 cm. H_2O for each breath, with a pulmonary ventilation of only 18 litres a minute, in comparison with the usual figure in normal individuals of 5 cm. H_2O pressure swing at rest, increasing to 40 to 50 cm. H_2O on effort causing dyspnoea with a pulmonary ventilation of 90 to 115 litres a minute. An additional factor decreasing lung distensibility in pulmonary oedema may be surface tension changes in the lung due to the presence of the sticky mucinous fluid in the air passages and the congested alveoli. Bronchospasm, which is often a striking clinical feature of acute pulmonary oedema, is an important contributory cause of the dyspnoea by increasing respiratory resistance. The bronchial veins drain either directly into the left atrium or into a main pulmonary vein, and swelling of their small tributaries lying in the submucosa of the bronchioles, caused by a high left atrial pressure, may contribute to the bronchial narrowing (Marchand *et al.*, 1950).

Summary

Studies on the formation and removal of oedema fluid in the lung show that in cardiovascular disease pulmonary oedema does not occur unless the left atrial and pulmonary capillary pressures exceed the effective plasma osmotic pressure by a considerable margin.

Exercise in patients with mitral stenosis or left ventricular failure produces circulatory changes identical with those found during attacks of acute pulmonary oedema. The fact that acute pulmonary oedema does not necessarily occur in spite of a high pulmonary capillary pressure suggests either that the fluid is hindered in its escape into the interstitial tissue of the lung and air passages by the structural changes in the capillary wall and alveolar epithelium, or that it is rapidly removed by the extensive pulmonary lymphatic system.

In acute attacks of pulmonary oedema, in addition to the high pulmonary capillary pressure some unknown factor, possibly neurogenic, may suddenly increase the capillary permeability. All those procedures which are effective in the treatment of the acute clinical attack lower the pulmonary capillary pressure, which is invariably raised during it.

Subacute pulmonary oedema due to uraemia, malignant hypertension, polyarteritis nodosa, and the "rheumatic lung" is characterized by clotting and organization of the interstitial and alveolar exudate, and is probably caused by a combination of left ventricular failure and altered capillary permeability.

The increased rigidity of the lung which occurs on exercise in patients with heart failure and is responsible for the increased respiratory effort when the patient is dyspnoeic, and the low minute volume of ventilation, may be caused more by interstitial oedema of the lung than by pulmonary capillary congestion.

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TREATMENT OF INTRACTABLE PAIN WITH LARGE DOSES OF MORPHINE AND DIAMINO-PHENYLTHIAZOLE

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Morphine given as its salts has the world-wide reputation of being the most effective agent for the relief of pain and associated mental anguish. Its use in large doses for the relief of severe pain, of either medical or surgical origin, has been hindered by the risk of producing severe respiratory depression.

To date, the only substances known clinically to be active in combating this respiratory depressant effect have been N-allylnormorphine ("lethidrone," "nalorphine," "nalline") and, more recently, levallorphan (Eckenhoff and Funderberg, 1954). Lasagna and Beecher (1954) have studied the analgesic potentialities of mixtures of morphine and nalorphine, but, to date, no satisfactory clinical combination of these two drugs has been found that, in adequate therapeutic doses, does not produce some toxic effect.

In this paper we wish to discuss the clinical use, in 35 cases, of a morphine antagonist—namely, 2 : 4-diamino-5-phenylthiazole hydrobromide (D.A.P.T.) (Davies *et al.*, 1950)—which, while having in therapeutic doses little effect on the analgesic properties of morphine, reveals marked and lasting antagonism to its respiratory depressant effect and thus renders the clinical use of large doses of morphine a safe procedure.

The use of D.A.P.T. as a morphine antagonist in animals has been previously reported (Shaw and Bentley, 1949, 1952; Shaw and Shulman, 1955), and D.A.P.T. has also been used as a synergist with $\beta\beta$-methylethylglutarimide (NP13, "megimide") in the treatment of barbiturate intoxication (Shulman *et al.*, 1955).

Pharmacology of D.A.P.T.

From the above animal experiments and from the clinical results obtained it would appear that the following are the facts of pharmacological importance regarding D.A.P.T.

1. It is a specific antagonist of morphine (Shaw and Bentley, 1955). It has been found to be specially effective in relieving the respiratory depression caused by excessive doses of morphine, heroin, "omnopon," and the synthetic analgesics, pethidine, and methadone hydrochloride. The depth of respiration is increased rather than the rate. It appears sometimes to antagonize the vomiting and, usually, the constipation associated with morphine.

2. It appears to be a non-specific respiratory stimulant, especially by the parenteral route. Its use in barbiturate poisoning has been discussed already (Shulman *et al.*, 1955).

3. Prolonged administration of large doses of morphine —1½–2 gr. (80–130 mg.) thrice daily—in the presence of D.A.P.T. demonstrated that these doses did not lose their analgesic effect—or, at the most, the morphine dosage had to be increased by 30%. We feel it would be unwise on this evidence to claim that D.A.P.T. prevents the onset of tolerance, but in our series (30 cases continuing, some up to five months) there were no signs of development of tolerance or addiction. In two cases the injection of large—2-gr. (130-mg.)—doses of morphine thrice daily enabled us to reduce the total daily requirement when this had been given in small—½-gr. (32-mg.)—amounts at frequent intervals.

4. Whereas therapeutic doses will anatagonize the respiratory depressant effect of morphine, an increase in the dosage will also anatagonize its soporific action. A still higher dosage may leave the patient awake and mentally restless. This may be associated with transient muscular twitches, prolonged and forced expirations, and occasionally vomiting. Mental disorientation has been produced occasionally in the aged.

5. It seems to have a high therapeutic index (about 10) when used in animals or clinically, either as a morphine antagonist or as a synergist to $\beta\beta$-methylethylglutarimide in the treatment of barbiturate intoxication. In the latter case doses of more than 0.5 g. have been given over a two-hour period with the production of neither acute nor delayed toxic symptoms.

6. It has no analgesic properties of its own when given by either the oral or the parenteral route.

7. Small doses have little effect on the blood pressure, but with a large intravenous dose (75 mg.) there may be a rise in blood pressure.

8. It is a stable white crystalline powder readily soluble in water (4%) at room temperature. Physiological solutions slowly hydrolyse, but refrigerated solutions have been shown to retain their activity for periods up to one week.

Some preparations of D.A.P.T. contain a toxic impurity, and it has been our practice to check all samples for toxicity by means of a "rat test"—that is, the LD_{50} of a standard pure sample is compared with that of the new preparation.

Treatment of Severe Pain

Principle.—Before the new treatment can be successfully applied it is essential to discard an ancient concept—namely, that morphine is a dangerous drug. Up till now the use of morphine has been attended by the immediate risk of respiratory depression and the long-term inconvenience of tolerance. Both these dangers are now banished by the use of the thiazole derivative. Accordingly it is recommended that the present practice of the administration of small dosages of morphine at frequent intervals be abandoned. One should aim at large—1–2-gr. (65–130-mg.)—doses of morphine, which are sufficient to produce an analgesia of six to eight hours' duration and which nevertheless still keep the patient alert. These doses should be given at the initiation of the treatment. The great psychological advantage of never having the patient suffer severe pain cannot be too strongly stressed. The principle of the treatment therefore consists in giving gradually increasing amounts—¼-gr. (16-mg.) increments—of morphine accompanied by D.A.P.T. (15 mg.) over a period of one (or two) days until the desired degree of analgesia is obtained.

Detail.—The patient will probably be receiving ¼–½ gr. (16–22 mg.) of morphine. In the following, "treatment" means the injection of both morphine and D.A.P.T. and

the subsequent observations of respiration, etc. Inject ½ gr. (32 mg.) of morphine, and 15 mg. of D.A.P.T. 30 minutes later—that is, when the maximum effect of morphine is being exerted—both injections being intramuscular. Observe respirations (and sedation) every 15 minutes for two hours. If the pain returns before the termination of six hours and the respirations have not fallen below 6–8 a minute, repeat the "treatment" with ¼ gr. (50 g.) of morphine and 15 mg. of D.A.P.T. (observe respirations as before). If the degree of respiratory depression should cause concern a dose of 10 mg. of D.A.P.T. may be repeated at 10-minute intervals (see Note 3). If the pain returns before the expiration of six hours, and the respirations have not fallen below 6–8 a minute, repeat the "treatment" with 1 gr. (65 mg.) of morphine and 15 mg. of D.A.P.T. (observe respiration as before).

At this stage pain of mild-to-moderate intensity should be receiving up to eight hours' relief per "treatment" without any undue sedation. The patient is now said to be stabilized.

In cases of very severe pain it may be necessary to give doses of morphine of up to 2 gr. (130 mg.) three or four times a day, in the following manner.

Inject 1½ gr. (90 mg.) of morphine and 15 mg. of D.A.P.T. (intramuscularly) and observe respiration, etc., as before. Repeat this "treatment" when pain returns or at the end of six hours. If the analgesia is still inadequate and the respirations have not fallen below 6–8 a minute give two "treatments" of 1½ gr. (100 mg.) of morphine and 15 mg. of D.A.P.T. If adequate analgesia is not obtained inject 2 gr. (130 mg.) of morphine and 15 mg. of D.A.P.T. When the patient has been stabilized, usually on the second day of treatment, the intramuscular injection of D.A.P.T. is replaced by the oral administration. A dose of 20 mg. (one tablet) of D.A.P.T. is given at the same time as the morphine injection. If the patient is unduly sedated during the day, the oral dose of D.A.P.T. may be increased up to 30 or 40 mg., and reduced to 20 mg. at night.

Notes

1. The plan of the procedure is simple. The patient is given graded doses of morphine (with D.A.P.T.) until respiratory depression (or sedation) is evident or an analgesia of from six to eight hours is obtained.

2. D.A.P.T. is an extremely safe drug. The dose is 15 mg. intramuscularly; as much as 100 mg. has been given without ill effect, but careful administration is advised as these high doses are approached.

3. Slow and irregular breathing is not a sign of respiratory danger, provided that the respirations are deep and cyanosis is not present. Under these conditions a rate as slow as 6 a minute is not dangerous. If at any time the respiration of the patient should cause concern—that is, if the rate should fall below 6–8 or the breathing be shallow, with cyanosis—further intramuscular injections of 10 mg. of D.A.P.T. may be made at 10-minute intervals until 60 mg. of D.A.P.T. has been given. It must be stressed that D.A.P.T. will increase the depth rather than the rate of respiration. For more rapid action the D.A.P.T. may be injected intravenously.

4. It has been found easier to prevent the onset of pain than to alleviate it once it has occurred. Accordingly it is better to give four treatments a day rather than three if pain tends to recur at about seven hours.

5. Care should always be exercised in the treatment of the aged.

6. At night it is desirable to give a barbiturate cover or an injection of hyoscine—1/150–1/100 gr. (0.43–0.65 mg.).

7. If the patient has not received sufficient relief from a large injection (over 1 gr.—65 mg.) of morphine it is safe to repeat the injection (with D.A.P.T.) at any time after two hours.

8. If the patient's condition worsens as death approaches and the period of analgesia shortens, the dose of morphine may be increased by ¼-gr. (16-mg.) increments. The need to increase the D.A.P.T. is unusual, but it may be increased by 5–10 mg. in the presence of respiratory depression or undue sedation.

9. D.A.P.T. given in therapeutic doses to a morphinized patient causes practically no side-effects. Slight irregular flickers of the fingers, shoulder, and neck were occasionally observed, but these could not be differentiated from identical movements seen in the drowsy and deeply morphinized patient to whom no D.A.P.T. had been given.

In some of our early cases morphine and thiazole were given cautiously by continuous intravenous therapy. Such procedure has not been necessary in our later cases.

The Concomitant Use of Other Drugs

There are no pharmacological contraindications to the use of the following drugs with D.A.P.T.

1. Hyoscine.—This drug in larger doses (1/100 gr. (0.65 mg.) intramuscularly) increases the drowsiness and may extend the period of analgesia. It should be used only at night or in cases of very severe pain.

2. Atropine has a similar action to that of hyoscine, but less marked.

3. Barbiturate.—This drug may be used where it is felt to be of benefit, especially at night if sleep does not come easily.

4. Chlorpromazine ("Largactil").—This drug has been used in about 10 of our cases. Vomiting is usually lessened and the period of analgesia increased, but the patient is much drowsier.

5. "Marzine."—This new anti-emetic has been used in six cases of hyperemesis. The vomiting is usually prevented until the terminal stages are reached, when it appears to lose its efficacy.

A brief synopsis of two of the 35 cases investigated appears below. Further summaries are given in Table I. A list of the dosages required for complete relief is given in Table II. In all but four cases these dosages remained unaltered until death supervened. In the four cases mentioned—dose 1–1½ gr. (65–80 mg.)—the dose had to be increased to 2 gr. (130 mg.) during the final two days.

TABLE I

Age and Sex (Years)	Condition	Before Treatment: Dose of Morphine gr.	mg.	Before Treatment: Duration of Analgesia (Hours)	Treatment: Morphine (gr.)	Treatment: D.A.P.T. (mg.)	After Treatment Duration of Analgesia (Hours)	Duration of Treatment (Weeks)	Comments
F 35	Ca. breast, oedema arm	½	22	2–3	2 I.M. q.d.	20–40 P.O.	6	18	Excellent relief of pain. No side-effects with large dose morphine over 4 months' period
F 42	Ca. cervix	½	22	2–4	1 I.M.	8 I.M.	8–12	2	
F 69	Melanoma of toe	¼	16	2	1 I.M. b.d.	8 I.M.	8–12	2	
F 65	Ca. breast, oedema left arm	¼	16	2	½ I.M. q.d.	20 P.O.	6–7	4	Slight mental disorientation due to secondary in brain or to morphine (?)
F 55	Ca. breast	½	22	1½	1 I.M. t.i.d.	20 I.M.	8	1	
F 55	,, femur	½	32	2	1 I.M. t.i.d. 2 I.M. (terminal two days)	20 P.O.	8	12	Complete relief from severe pain. No side-effects
F 85	Gangrene left foot	⅛	11	2–4	1 I.V. 1 I.M.	6 I.V. 4 I.M.	10–12 6–10	2 2	8 mg. D.A.P.T. gave signs of mental disorientation in old patient
F 52	Ca. colon	½	32	2	2 I.M. q.d.	20–40 P.O.	6–7	10	Slight double vision due to large dose of morphine
F 78	,, breast	¼	16	1	½ I.M. t.i.d.	20 P.O.	8	13	No mental disorientation
F 55	,, femur	¼	16	2	1 I.M. t.i.d.	40 P.O. (day); 20 P.O. (night)	8	12	Hospitalized at commencement. One month later returned home

TABLE II

Dose of Morphine to Give 8 Hours' Analgesia	No. of Patients Receiving Relief
¼ gr. (32 mg.)	2
⅜ „ (48 „)	3
½ „ (65 „)	8
1 „ (77 „)	10
1¼ „ (110 „)	6
1½ „ (130 „)	5
2 „ (160 „)	1
	35

Case 1.—A woman aged 52 had cancer of the lower jaw with extensive metastases and was greatly emaciated. When seen she was receiving 8 gr. (0.52 g.) of morphine a day, in divided doses, with less than two hours' relief from pain. Vomiting and constipation were troublesome. The patient was stabilized with 1¼ gr. (110 mg.) of morphine and 15 mg. of D.A.P.T. intramuscularly. During the next two days she was free of pain for six hours at a time and the vomiting and constipation were relieved. The dosage of morphine was then increased to 2 gr. (130 mg.) and 20 mg. of thiazole was given orally. Pain was relieved for eight hours, and she did not feel drowsy. The treatment continued for five weeks until the patient died. There were no untoward symptoms other than a transitory mild mental disorientation. This disorientation has been observed in other cases: it is mild and transitory, and appears to be due to the large doses of morphine rather than the D.A.P.T., as it has been observed only in the older patients.

Case 2.—A woman aged 38 with cancer of the breast, marked oedema of the left arm, and intolerable pain received no more than two hours' relief from ¼ gr. (16 mg.) of morphine. Treatment was begun, and the patient stabilized, on 1¼ gr. (110 mg.) of morphine and 15 mg. of D.A.P.T. intramuscularly three times a day. There was complete absence of pain with a decrease in the incidence of vomiting, and the constipation was rectified. On the fourth day oral administration of D.A.P.T. (20 mg.) was substituted for intramuscular injection. Later the dose of D.A.P.T. given during the day was increased to 40 mg. at each "treatment" to combat slight sedation (the nightly dose remained at 20 mg.). Two months later the dose of morphine had to be increased to 2 gr. (130 mg.) three times a day; it is impossible to say whether this was due to development of tolerance or the increasing severity of the pain. There were no untoward side-reactions. The patient died after 18 weeks' treatment.

At the beginning of treatment this patient was very depressed. About one week after initiation her mood changed to one of cheerfulness and remained so until within one week of death. In about one-quarter of our cases we have noticed this favourable change in outlook. It does not appear to be a euphoria due to the morphine, but rather owes its origin to the D.A.P.T. This aspect is still under investigation.

Discussion

The adequate relief of prolonged and severe pain still remains one of the unsolved problems of medicine. To date, morphine and its analogues have been the drugs used, and these have been only partially effective in producing relief from severe pain. This is due to the fact that it has not been possible to administer sufficiently large doses to produce complete analgesia without evoking dangerous and undesirable side-effects such as respiratory depression, tolerance, vomiting, and constipation; especially in old and cachectic patients with poor hepatic and renal function.

The method here described, incorporating the use of 2:4-diamino-5-phenylthiazole hydrobromide (D.A.P.T.), permits the use of large doses of morphine, adequate to effect satisfactory analgesia, without the associated production of these dangerous and undesirable side-effects.

Special mention must be made of the apparent ability of D.A.P.T. to prevent or delay the onset of tolerance. This clinical observation, if substantiated by further work in progress, would make the action of D.A.P.T. unique in this regard.

As it is rare to have the opportunity of safely administering doses of morphine of the order of 1–2 gr. (65–130 g.) in a single injection, the following few points of physiological interest arising therefrom are worthy of mention.

The slow intravenous administration (20 minutes) of 1 gr. (65 mg.) of morphine sulphate with 1/150 gr. (0.43 mg.) of hyoscine hydrobromide exerts its maximum clinical effect within 20 minutes. Given intramuscularly, the full effect is not exerted for 40 minutes. These observations are also borne out in dogs under electroencephalographic control.

The slow intravenous or intramuscular administration of 1 gr. (65 mg.) of morphine sulphate and 1/150 gr. (0.43 mg.) of hyoscine hydrobromide usually has little depressant effect on the blood pressure or pulse rate. An occasional fall in the systolic pressure of 5–15 mm. Hg, associated with a transient pallor of the skin and a subjective feeling of cold, is sometimes observed, but this is quickly followed by a warm, flushed, and slightly sweaty skin with a return to normal blood pressure and an accompanying subjective feeling of warmth.

It would be natural to compare the action of D.A.P.T. with that of N-allylnormorphine (nalline). A full clinical comparison will be given in a later paper (Shulman, in preparation).

Nalline by itself has certain opiate properties and is not free from undesirable side-reactions when given in therapeutic doses (Payne, 1954; and several others). D.A.P.T. in doses at least five times the therapeutic is almost without side-reactions of any kind.

Nalline produces withdrawal symptoms in patients who have received only a few doses of morphine. This we have never observed with D.A.P.T. in therapeutic cases. Indeed, if it were so, our method of treatment of intolerable pain would not be possible, as all our patients had been receiving morphine before the beginning of treatment.

Nalline itself may cause vomiting, and does not appear to antagonize that due to morphine.

Nalline would appear to antagonize the analgesic action of morphine. This is certainly not the case with D.A.P.T. in therapeutic doses. Lasagna and Beecher (1954) have tried unsuccessfully to evolve a combination of nalorphine and morphine in post-operative patients and healthy volunteers which would give the desired therapeutic effect of analgesia without the concomitant production of the associated unpleasant side-reactions of morphine, and have discussed the difficulties involved in obtaining such a clinically useful mixture.

In addition to the extensive series of cases given above, D.A.P.T. has been used in a few cases of neonatal asphyxia, in methadone hydrochloride poisoning, and for the relief of post-operative pain. In the last-mentioned example the ability of the patient to cough painlessly was important. It should now be possible to use larger doses of morphine pre-operatively in conjunction with D.A.P.T., perhaps by intravenous administration. Finally, the removal of the risk of respiratory depression due to morphine should lead to an extension of this drug's use in the fields where it is already of value—namely, "shock," coronary occlusion, obstetrics, etc.—and may open up new fields in anaesthesia.

We wish to express our thanks to the superintendent and staffs of the Alfred, Austin, Royal Melbourne, and Women's Hospitals, and the Peter MacCallum Institute, Melbourne, for their kind co-operation in this investigation. We are indebted to Professor W. Davies, of the Chemistry Department of the University of Melbourne; Mr. E. T. Rosenblum, of Felton Grimwade and Duerdins Pty., Ltd. (Melbourne); Monsanto Chemicals (Australia) Ltd., and Nicholas Pty. Ltd. (Australia) for their gifts of 2:4-diamino-5-phenylthiazole hydrobromide. We are most grateful to Miss M. Bell, Miss S. Loewe, Miss M. Parker, and Mr. W. Straffon for their kind assistance with this work. Finally, we especially wish to express our thanks to Professor R. D. Wright, Dr. Kaye Scott, and Dr. W. P. Holman, for their kindly interest and advice during this investigation. This work was partly aided by a grant from the National Health and Medical Research Council of Australia.

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BLOOD CHOLINESTERASE VALUES IN EARLY DIAGNOSIS OF EXCESSIVE EXPOSURE TO PHOSPHORUS INSECTICIDES

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The phosphorus insecticides are a group of substances which owe their high mammalian toxicity to their inhibitory action on the enzyme cholinesterase located in the central and peripheral nervous system. Precautions to protect those engaged in the application of these insecticides are prescribed by the Agriculture (Poisonous Substances) Regulations, 1953, and similar action should be taken with regard to those engaged in their manufacture. If the precautions taken are inadequate, or are temporarily relaxed, the first sign of excessive exposure will be a diminution of the activity of cholinesterase circulating in the blood. Several surveys of the blood cholinesterase values of large groups of normal individuals have been published; these are necessary in order to provide a standard of reference whereby abnormally low values may be recognized. The results obtained reveal a wide scatter in both the plasma and the red-cell enzyme activities, though the coefficients of variation obtained by the various authors are consistent with one another (Callaway, Davies, and Rutland, 1951; Wolfsie and Winter, 1952; Fleisher and Pope, 1954).

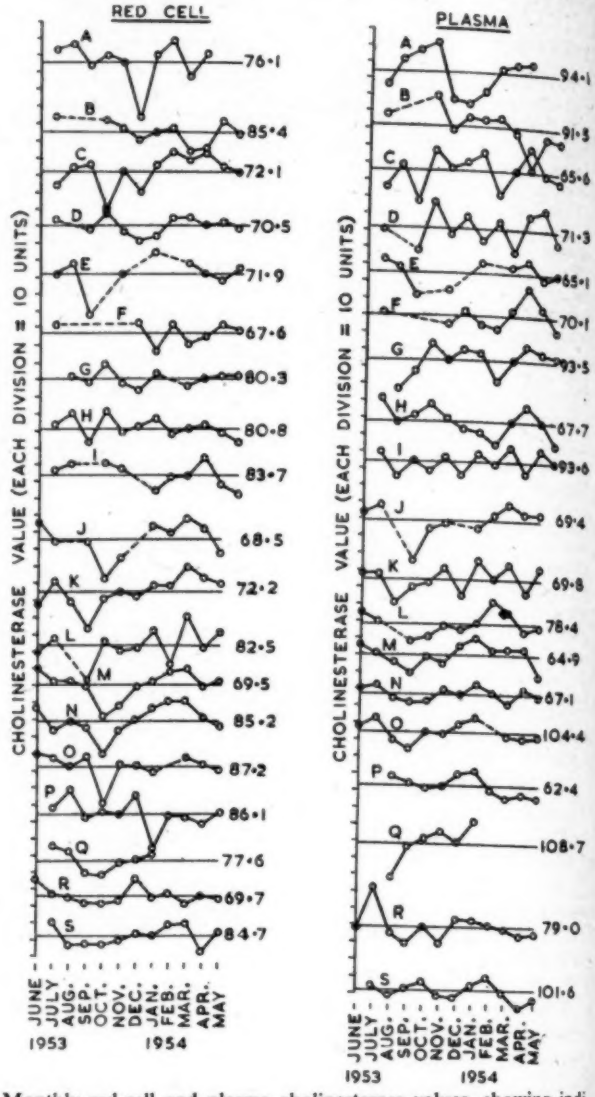
Callaway *et al.* (1951) have suggested that a better indication of a significant fall in blood cholinesterase activity would be obtained if a measurement on an individual is referred, not to the average value of a normal population, but to a series of readings on the same individual prior to exposure to an anticholinesterase, and they have recommended a statistical procedure for doing this. The present investigation was undertaken to extend this treatment by a study of the nature of the temporal variation of cholinesterase activity in normal individuals and thereby to establish criteria for the recognition of significantly low blood cholinesterase values.

Experimental

The selection of the individuals who took part in these tests was not random. Volunteers were requested, and from those who offered themselves were selected the ones who showed the widest range of cholinesterase values. The sex and occupations of the subjects are shown in Table II. The technique of taking finger-tip blood samples and the procedure for measuring cholinesterase activity were similar to those used by Wolfsie and Winter (1952); wherever possible, duplicate blood samples were taken to permit the calculation of the experimental error. The tests were made only when the subjects were in sufficiently good health to continue their normal employment, and none at any time came into contact with phosphorus insecticides or any other known cholinesterase inhibitor.

Experimental Results.—The results obtained from the cholinesterase measurements are displayed graphically in the Chart. Where duplicate blood samples were available, the points on the graphs are the mean of the pairs of determinations.

Experimental Error.—For the calculation of the experimental error, 119 duplicate pairs of red-cell samples and 135 duplicate pairs of plasma samples were available. From these duplicate measurements red-cell and plasma variances due to combined sampling and measurement error were found to be 24.3 and 33.3 respectively, corresponding to



Monthly red-cell and plasma cholinesterase values, showing individual average values. The reference letters correspond with those in Table II.

standard deviations of 4.93 and 5.77. In order, therefore, that two single determinations should be regarded as significantly different ($P=0.05$) they must differ by at least 14 units for red cells and 16 units for plasma, or, if the averages of duplicate determinations are being compared, by 10 and 12 units.

Monthly Averages and Variances

Table I shows the averages of the monthly groups of determinations and the monthly variances which are a measure of the variation of the individual values within these groups. There is no evidence to suggest, and no reason to suppose, that these variances are not homogeneous, and the combined variance within the monthly groups can be shown by the usual method of analysis of variance to be 99 for red cell and 283 for plasma. These two terms are a measure of the scatter of cholinesterase activities in normal individuals; the coefficients of variation derived from them are 12.8 and 21.3 respectively, which are within the range of the figures quoted by Callaway *et al.*

TABLE I.—*Monthly Averages and Variances*

Month	Red Cell		Plasma	
	Average	Variance	Average	Variance
June, 1953	79·7	92·1	79·6	185·8
July	82·3	69·6	83·3	297·0
August	75·6	145·0	75·2	376·6
September	76·1	192·4	81·6	425·8
October	72·3	138·8	77·6	297·3
November	71·9	146·8	80·2	257·4
December	79·2	93·0	80·7	271·3
January, 1954	80·0	62·9	82·0	366·0
February	77·4	71·4	78·8	246·2
March	82·2	105·5	81·1	190·1
April	77·9	49·5	76·8	194·5
May	76·1	78·7	73·6	254·2

A comparison of the monthly averages gives no indication of any real seasonal variation in the cholinesterase values, nor any change in the quantitative interpretation of the method of measurement. Analysis of variance does not conflict with this impression; there is no evidence of any significant difference between the monthly averages of the plasma values, while the red-cell averages show a difference with a low order of significance (P between 0.05 and 0.1).

Individual Averages and Variances

It is evident that if a series of measurements of a variable property, such as enzyme activity, are made on an individual, the results will approximate more closely to one another the shorter the interval between the measurements. As the interval increases, the dependence of a result on that of the previous determination decreases, and when the interval exceeds any periodicity in the fluctuation of the enzyme activity the results will be scattered randomly round the average value. An inspection of the graphs in the Chart reveals that this interdependence or serial correlation does occur to some extent and is manifest by a secular drift around the average value, but it is broken up by completely random variations. The individual variances reported in Table II range between 165 and 18.8 for red cell and 158

TABLE II.—*Individual Averages and Variances*

Reference	Occupation	Sex	Red Cell		Plasma	
			Average	Variance	Average	Variance
A	Packer	M	76·1	164·7	94·1	158·3
B	Bricklayer	M	85·4	42·6	91·5	124·3
C	Process worker	M	72·1	95·8	65·6	101·9
D	Engineer's labourer	M	70·5	27·0	71·3	100·9
E	Plant superintendent	M	71·9	103·3	65·1	57·8
F	Joiner	M	67·6	35·4	70·1	62·1
G	Warehouseman	M	80·3	18·8	93·5	73·8
H	Production supervisor	M	80·8	57·5	67·7	72·7
I	Process worker	M	83·7	53·1	93·6	35·9
J	Bricklayer	M	68·5	119·4	69·4	92·7
K	Plant superintendent	M	72·2	85·6	69·8	58·9
L	Production supervisor	M	82·5	102·6	78·4	47·2
M	Laboratory assistant	F	69·5	66·3	64·9	47·8
N	Laboratory assistant	F	85·2	78·3	67·1	15·3
O	Office worker	M	87·2	64·5	104·4	33·0
P	Instrument maker	M	86·1	77·2	62·4	32·7
Q	Joiner	M	77·6	41·6	108·7	126·7
R	Boilerman	M	69·7	25·3	79·0	75·6
S	Maintenance fitter	M	84·7	34·7	101·6	45·0

and 15.3 for plasma cholinesterase. The Bartlett test fails to show any significant difference between these variances; the conclusion should not be drawn from this that the variances are equal for all individuals, but that the evidence is not sufficient to discriminate between them. Nevertheless, the usual method of analysis of variance is sufficiently valid, and this reveals the expected highly significant differences between the individual averages, although the scatter of these averages is considerably less than that of single determinations.

The variance between the groups of individual figures, calculated by analysis of variance, may be regarded as an estimate of the variance of the basic individual red cell and plasma values, independent of temporal variation; these variances were calculated to be 43 and 211 respectively. These figures give rise to coefficients of variation of 8.4 and 18.3 compared with 12.8 and 21.3 derived from the variances of single individual values quoted above. These observations demonstrate that the scatter of single enzyme measurements on a large number of individuals derives from differences in the basic cholinesterase activities of the individuals, amplified by the deviations from these basic values which operate at the time of measurement. These deviations are themselves compounded of the variation due to experimental error and temporal changes in the blood cholinesterase activity due to causes at present unknown. There is an indication from the graphs in the Chart that for most individuals the same general trends exist in the temporal variation of both red-cell and plasma cholinesterase, yet there is clearly no close correlation between them.

The method derived by Callaway *et al.* for the recognition of significant decreases in blood cholinesterase activity may now be examined in the light of the above observations. These authors considered that the significance of the deviation of a value from the mean of n previous values on the same individual is given by the expression $s\sqrt{(n+1)/n}$, where s is an estimate of the standard deviation of the distribution of values round the individual average; s was calculated from repeated measurements of the blood cholinesterase activity of a limited number of young Service men. This treatment is based on the assumptions that the individual values are randomly scattered round the individual averages and that the variances are homogeneous, both of which are not entirely in accordance with the experimental findings described above. An alternative statistical treatment of the results, involving an attempt at a mathematical study of serial correlation, can hardly be justified, as all the information contained in the experimental figures which is relevant to the application of these cholinesterase measurements may be extracted from the Chart by inspection.

Criteria for the Assessment of Excessive Exposure

From the information derived from the present investigation it is possible, when confronted by one or more cholinesterase values in an individual, to form an opinion whether the values are so much below the average value for the population or a decrease between two successive readings is so large that an abnormal fall in blood cholinesterase activity has occurred. Such a procedure would enable the non-observance of safety precautions, or faulty operation of plant or of apparatus used in the production or application of phosphorus insecticides, to be deduced from blood cholinesterase measurements on those engaged on these operations. If, however, the tests are regarded as a method of diagnosis of the early stages of poisoning and as a means of deciding whether a man should or should not continue in his employment, then it is necessary to define a value below which the symptoms of poisoning may be expected to manifest themselves. This is a matter of considerable difficulty, as there is little agreement in the literature on this point (Garlick, 1950; Brown and Bush, 1950; Grob, Garlick, and Harvey, 1950; Barnes and Davies, 1951; Williams and Griffiths, 1951; Kay *et al.*, 1952).

Moreover, there is evidence that a man with a decreased cholinesterase value may remain without symptoms and yet be in a hypersensitive state which will cause him to react strongly to a further absorption of the anticholinesterase, to which, in the absence of a previous exposure, he would not be susceptible (Davies and Nicholls, 1955). It is therefore desirable, when there is reason to suspect an abnormally low value, not only to search for the cause but to remove the subject from the range of the phosphorus insecticide until his blood cholinesterase value has returned to normal.

In applying cholinesterase measurements to control the manufacture and use of phosphorus insecticides it is understandable if, in order to gain a larger margin of safety, somewhat narrower limits of normality are defined than the experimental evidence justifies, and a number of normal individuals are thereby classed as victims of excessive

exposure. Yet it must be remembered that this method will fall into disrepute, and lose that energetic co-operation from management and men which is essential to it, if men are too frequently taken off work or there is an interruption of production or application processes when no clinical symptoms are apparent, nor any evidence of unsatisfactory working conditions.

Owing to differences in technique and in the definition of units it is not always possible to make direct comparisons between cholinesterase activities measured in different laboratories. Nevertheless, the ratio between two values determined in the same laboratory should be comparable; a statistic such as the coefficient of variation, which is itself a ratio, can be regarded as a property of the population under investigation and independent of variations in technique. In order that the deductions from the present investigation should be generally applicable, all quantitative terms have been presented as ratios based on the relevant average value for the population; and before any laboratory can apply these or any other recommendations of a like nature it is necessary that an adequate estimate of this statistic should be determined. This should be based on cholinesterase determinations on as many randomly selected normal individuals as possible; the number should not be less than 20.

The approach to the significance of a single blood cholinesterase measurement on an individual varies according to the previous history of cholinesterase measurements. If no value previous to contact with phosphorus insecticides is recorded, then the distribution of single measurements of cholinesterase activity on a normal population must be invoked. The present investigation gives population averages of 77.7 and 79.2 for red-cell and plasma cholinesterase values respectively, with standard deviations of 9.9 and 16.8. There is therefore a one in forty chance that a normal individual will have a plasma and red-cell cholinesterase value less than 57.8 and 45.6—that is, 74.3% and 57.5% of the average values respectively. It is suggested that if a red-cell or plasma cholinesterase value of an individual in contact with phosphorus insecticides is found to be less than one-half of the population average, it should be regarded as a sign that appropriate action should be taken—that is, he should not be allowed to continue in his employment and the process and precautionary measures should be carefully scrutinized. If a value between 50% and 60% of the population average is encountered it should be regarded as an alerting signal to stimulate an active supervision of the process; in particular, frequent blood cholinesterase measurements should be made in those concerned in the process. If the single cholinesterase determination has been made in order to confirm suspected symptoms of anticholinesterase poisoning, then there need be no hesitation in accepting a value below 60% of the population average as confirmatory evidence.

The procedure just outlined is bound to miss small but significant decreases in cholinesterase in subjects whose normal activity is high. If one or more pre-exposure values on an individual are known, these provide some indication of the individual's normal value, and it seems desirable to modify the above recommendations by requiring that appropriate action be taken if an individual is found to have a cholinesterase value one-half of the population average or one-half of the average of his pre-exposure values, whichever is the higher.

Regular Testing

The most desirable procedure is the regular testing of all individuals engaged upon, or likely to be engaged upon, the manufacture or handling of phosphorus insecticides. From an inspection of the graphs obtained by plotting the results obtained from such regular tests, the pattern of the normal cholinesterase values may be determined and any departure therefrom recognized. The individual graphs of the Chart reveal drifts around the individual average interspersed with random fluctuations of varying magnitude. In no case is any value inferior to that of the previous month by more than 30 units, nor are any of those approaching this value maintained into the subsequent months. It is recommended, therefore, that if in such a systematic series of tests a decrease of more than 40% of the population average is encountered it should be regarded as a reason for taking the appropriate action defined above, and if the fall is between 30 and 40% of the population average then supervisory measures should be made stricter. There is not sufficient evidence to indicate the extent of any likely downward drift in normal individuals, but it is suggested that the condition should be suspected if the value approaches 60% of its pre-exposure value.

The separate determination of red-cell and plasma cholinesterase has been stated to present a diagnostic advantage in cases of poisoning by anticholinesterases (Grob *et al.*, 1950). If the experimental procedure is restricted to the enzyme activity of whole blood there is a considerable saving of time; the criteria suggested above would equally apply to such measurements.

Summary

The red-cell and plasma cholinesterase values of 19 normal individuals have been measured at monthly intervals for a period of one year. The distribution of the monthly values on each individual is not entirely random, there being some measure of serial correlation. There is no clear evidence of any seasonal variation in the values.

The distribution of all the values on all the individuals has a coefficient of variation of 12.8 and 21.3 for red cell and plasma respectively. The contributory factors to this variation are discussed, and it is shown to be compounded of a basic individual variation, increased by the experimental error of measurement and individual temporal variations of unknown origin.

The establishment of limits of cholinesterase activity, whereby excessive exposure to phosphorus insecticides may be recognized, is discussed.

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Claimed to be Britain's first secondary school for spastics, the Thomas Delarue School was opened recently by the National Spastics Society at Dene Park, Tonbridge, Kent. This is the first of five special schools which the Society and its groups will open this year. Eighteen children from a number of towns and cities in England and Wales will be admitted to the Thomas Delarue School this term, and it is hoped eventually to accommodate 45 handicapped boys and girls. Education up to general certificate level, combined with treatment, will be provided. A second school was opened on May 11 at Craig-y-Parc, Cardiff. Twelve children aged from 5 to 16 from towns and cities in Wales and the West of England will be the first pupils, but it is hoped that facilities will eventually be available for 35 to receive education and treatment.

A FIELD TEST FOR THE ASSAY OF HUMAN WHOLE-BLOOD CHOLINESTERASE

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The level of cholinesterase (ChE) in the blood is a valuable index of the amount of anticholinesterase which has been absorbed into the system, and it has in fact been used for this purpose (Metcalf, 1951; Davies, 1952a; Marchand, 1952). Since anticholinesterases are being used extensively in agriculture and for insect vector control—very often far removed from laboratory facilities—the determination of such an index under field conditions would be useful. The essential requirement of a field test is simplicity. The procedure and equipment required should be simple, few reagents be necessary, and the time taken for the performance of the test be reduced to a minimum. Finally, the test should be sufficiently uncomplicated to be carried out by non-specialist personnel.

Aldridge and Davies (1952) have discussed the possibility of applying the generally used techniques for ChE assay to field conditions, and came to the conclusion that, for reasons given, these were unsuitable. They did, however, suggest that the electrometric method of Michel (1949) was satisfactory under certain circumstances. They based their suggestion on the fact that this technique lent itself to the rapid and easy estimation of considerable numbers of samples. While subsequent experience has shown this to be true, there are two major disadvantages. The *p*H meter is not reliable enough to use in the field; and the glass electrode is most certainly too fragile for this purpose.

Fleisher and Pope (1954) have applied the Hestrin (1949) colorimetric method to the estimation of whole-blood ChE. Their method possesses the advantage that it is a colorimetric technique and that single estimations can be completed, including the collection of the blood sample, in twenty-five minutes. Its disadvantages as a field test are (1) relatively few tests can be performed in a given time, and (2) at least six reagents and an equally large number of manipulative processes are involved. Furthermore, the technique requires the use of a spectrophotometer.

Limperos and Ranta (1953) have described a test which they have used under field conditions and which approximates to the requirements. The principle is the same as that of the electrometric method. The differences are (1) that changes in *p*H are followed by changes in a bromthymol blue (B.T.B.) solution incorporated in the reaction mixture, and (2) the test is carried out in an unbuffered medium. The levels of enzyme activity are assessed by the colour of the solution after a given interval of twenty minutes, and these colours are green, olive green, olive brown, and orange. In practice the distinction between the first two and the second two is difficult. This is a serious disadvantage, since (as is shown below) this is the important range. A second major disadvantage is that under certain conditions of illumination the combination of blood and B.T.B. appears to fluoresce. When this happens colour assessment is almost impossible. Despite these difficulties a relatively slight modification of procedure has been shown to give a workable and satisfactory test. If a fixed colour change is taken—for example, from green to orange—and the time for the change to occur is observed, these difficulties are overcome.

Experimental

Apparatus.—Tubes 3 by ⅜ in. (7.5 by 1 cm.) (one for each test). Pipettes: 10 ml. graduated in 1 ml.; 5 ml. graduated in 0.5 ml.; 20 c.mm. haemoglobin pipette. Rack to hold ten 3 by ⅜-in. tubes. Watch to read accurately in minutes. Triangular needles, 1 packet. Thermometer.

Reagents.—Two solutions only are needed. (1) Acetylcholine chloride ampoules (Roche Products), 0.6% solution. Dissolve the contents of six 0.1-g. ampoules in 100 ml. of distilled water. This solution can be stored at 20° C. for a period of five or six days without deterioration, and provides sufficient solution for 200 tests. (2) Bromthymol blue: (*a*) Stock solution, 0.04 g. of powder is dissolved in 1 ml. of N/20 sodium hydroxide. Approximately 90 ml. of distilled water is added and then sodium hydroxide, dropwise, until the solution just turns blue. The total volume is made up to 100 ml. The *p*H of this solution should be 7.7, and if it is possible, since this solution can be made up in the laboratory, it should be checked with a *p*H meter. (*b*) For use, dilute two volumes of stock solution with one volume of distilled water.

Technique.—Collect 20 c.mm. of blood in a haemoglobin pipette and wash it out into 1 ml. of dilute B.T.B. solution contained in one 3 by ⅜-in. tube. Add 0.5 ml. of acetylcholine chloride solution and note the time of addition. Note the exact time at which the colour of the reaction mixture becomes deep orange. The interval is a measure of the enzyme activity. To facilitate the determination of the end-point, a standard* is easily prepared as follows: Blood and B.T.B. solution in the above proportions are added to a tube and then 0.15 ml. of N/100 acetic acid. The volume is then made up to 1.5 ml. (The *p*H should be 6.7.)

Results

If the time interval over which the requisite colour change occurs is determined precisely, then the assessment of whole-blood activity correlates closely with determinations made by the electrometric method. This is shown in Fig. 1. In this figure the reciprocal of the time (T) taken to effect the given colour change at temperature (t) is plotted against the activity of the sample in △*p*H/hour always determined at 25° C. (For convenience the actual △*p*H value has been multiplied by 100 throughout.) In this case t was between 19 and 22° C. The close correlation between △*p*H/hour and T is obvious from the graph.

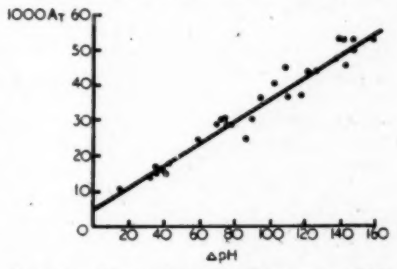

FIG. 1.—The relationship between ChE activity measured as (1) the reciprocal of the time necessary to effect given colour change (that is, A_T), and (2) in electrometric units (that is, △ *p*H). A_T determined at temperatures between 19 and 22° C., △ *p*H determined at 25° C.

The relative activities of different specimens at varying temperatures have been plotted against the temperature, the activity at 20° C. being taken as equivalent to 100. The relative activity increases with temperature in a non-linear fashion from 10° to 40° C. Above 40° C. results become uncertain. At 10° C. the relative activity is about 65, whilst at 30° C. it is 137.

*A permanent glass standard is obtainable from Tintometer Ltd., Salisbury.

The information yielded by these two series of experiments allows us to simplify the test for field conditions. If in addition it is possible to relate enzyme levels to zones which will permit clear-cut executive action, then a very useful test may be evolved. The latter idea is possible, for three critical levels of whole-blood ChE can be defined: (1) The lower level of normal whole-blood ChE activity; (2) the level of hypersensitivity; (3) the clinical danger level.

Lower Level of Normality.—There have been very many determinations of normal values of red-cell, plasma, and whole-blood ChE, and the limits of variation have been extensively worked out (Callaway *et al.*, 1951; Wolfsie and Winter, 1952; Fleisher and Pope, 1954). These are consistent with each other. For the present purpose the values for the whole-blood ChE as determined in this laboratory have been used to define the lower limits of normal activity. On a recently determined series the mean value of whole-blood ChE was 133 ($\triangle$ *p*H/hour) with a standard deviation of 12 ($\triangle$ *p*H/hour). The lower fiducial limit of normality is therefore 109 ($\triangle$ *p*H/hour).

Level of Hypersensitivity.—No symptoms of systemic poisoning are obvious until a very significant reduction of the blood ChE has occurred. Callaway *et al.* (1954), however, have shown that when the whole-blood ChE of rabbits has, by previous exposure to anticholinesterase, been reduced to half the pre-exposure value, there is a significant reduction in the LD_{50}, thus demonstrating that a reduction in the blood ChE level is indicative of an increased sensitivity towards further doses of anticholinesterase. Their data did not permit an extrapolation which would have indicated the exact point at which this increased sensitivity is first obvious. In the absence of such precise data, and bearing in mind the main purpose for which this test is being evolved, we therefore suggest that the level of clinical significance could be set at 50% of the mean normal level—that is, at $\triangle$ *p*H/hour of 67.

Clinical Danger Level.—Davies (1952b) noticed that the blood cholinesterase of animals dosed with anticholinesterase by the intravenous, intramuscular, or percutaneous route had to be reduced to at least 20% of normal before the onset of serious clinical symptoms. In his experience the critical whole-blood cholinesterase level is about 20% of normal, although it does not follow that symptoms automatically appear when this level of blood cholinesterase is reached (Frawley *et al.*, 1952). The clinical danger level may therefore be set at 20% of the mean normal level—that is, at $\triangle$ *p*H/hour of 26 units.

Effect of Temperature

The most difficult problem has been to evolve a method of temperature compensation without the use of a constant temperature bath or enclosure. This was done as follows. As indicated above, several simultaneous observations were carried out on the same sample at various temperatures, together with electrometric determinations at 25° C. These results were then summarized in a family of straight lines corresponding to each temperature and relating $1{,}000/A_T$ and $\triangle$ *p*H/hour, where T is the time taken for the completion of the colour change. From these, T was determined for each critical level at varying temperatures, and a new family of curves constructed relating T and temperature. By plotting these on one diagram, as in Fig. 2, a chart showing various zones has been constructed, each zone corresponding to the interpretation shown on the right side. (See also Table I.)

TABLE I

	Lower Level of Normality $\triangle$*p*H 109	Upper Level of Hypersensitivity $\triangle$*p*H 67	Level of Serious Poisoning $\triangle$*p*H 26
10° C.	41 minutes	63 minutes	111 minutes
15° C.	32 ,,	49 ,,	98 ,,
20° C.	26 ,,	40 ,,	87 ,,
25° C.	22 ,,	34 ,,	74 ,,
30° C.	19 ,,	30 ,,	62 ,,
35° C.	14 ,,	23 ,,	53 ,,

The *modus operandi* of the test is therefore as follows: The temperature of the ambient air is noted. An ordinate of the chart is then drawn corresponding to this temperature, and the time read off at the point where it cuts each curve.

The tubes are prepared as described earlier—that is, 1 ml. of B.T.B., 20 c.mm. of blood, and 0.5 ml. of acetylcholine chloride—and then the colours noted at each of these times, obtained from the chart (Fig. 2). In all the tubes in which the colour has changed to deep orange at the time of inspection the reaction is complete. For example, if the temperature was 23° C., the test with all normal blood samples would be complete in 21 minutes. Blood which changed colour in less than 34 minutes but longer than 21 minutes would possess whole-blood ChE levels lower than normal, and the level would indicate a slight absorption of anticholinesterase. Such levels would, however, be of little clinical significance. They would, on the other hand, indicate indifferent safety procedures or personal carelessness on the part of the individual.

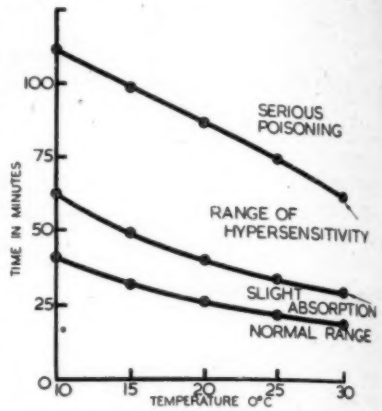

FIG. 2.—Chart relating time of colour change with temperature and degree of poisoning.

If the time taken is longer than 34 minutes this indicates that the individual is hypersensitive, and will come into the appropriate zone. If even after 72 minutes the test is not complete, at least 80% inhibition is indicated, implying danger of clinical symptoms.

It should be emphasized that an exact colour match with the standard is seldom necessary, since the criterion at the critical time is whether the colour change is complete at that time.

One other point with reference to temperature needs to be discussed. The test may in extreme circumstances—that is, at 10° C.—take 100 minutes to complete, and if no constant temperature bath is to be used it is rather important to know what temperature fluctuation may be permitted during the period of the test itself. The experiments on which the relationship between field test and the electrometric method (shown in Fig. 1) were based were carried out at 19° C., 20° C., and 22° C., hence a variation of 3° C. during the period of the test would seem to be permissible. Lowry *et al.* (1954) confirm this suggestion, for they state that to measure cholinesterase to within 3% the permissible temperature range is 3° C. This is, however, a point that ought to be checked under a wide variation of conditions, or at least kept in mind during the period of the test.

A series of experiments were carried out at different temperatures to check the chart that has been produced. The procedure was exactly as described. Forty-eight samples of blood were prepared by diluting normal blood with inactivated blood. Thirty samples (obtained from eight individuals) were examined on different occasions in the climatic chamber at 31° C. and 85% relative humidity. A further 16 samples (from four individuals) were tested in a constant temperature bath at 31° C. The results are shown in Table II.

Of the 47 samples so tested, 45 conform precisely to the pattern described in the test. Of the discrepant samples those with $\triangle$ *p*H/hour -116, $T_{31°} - 19$ minutes are only just outside the expected zone. A sample of $\triangle$ *p*H -116 should have a reaction time of 18 minutes or less.

TABLE II.—*The Confirmation of Reaction Times at 31° C.*

Normal Range		Range of Slight Absorption		Hypersensitive Range	
ΔpH hr.–109		ΔpH/hr.–109–67		ΔpH/hr.–67–26	
$T_{31}°$	18 min.	$T_{31}°$	18–29 min.	$T_{31}°$	29–67 min.
130	15	108	20	66	31
126	15	104	20	63	32
146	14	103	21	59	42
132	15	103	20	58	39
123	15	102	20	56	40
140	14	100	22	55	33
129	15	100	22	53	40
148	15	96	22	52	40
136	16	95	23	49	35
133	15	88	23	36	47
127	15	87	23	36	50
146	15	85	26	33	50
116	19	81	25	30	52
116	19	78	27		
110	18	76	27		
		75	27		
		75	28		
		73	28		
		67	27		

ΔpH/hour values and reaction times grouped according to the clinical zones described in Fig. 2.

Summary

The field test of Limperos and Ranta for the assay of human whole-blood ChE has been modified to facilitate its more extensive use. A chart has been constructed which permits adjustments in the conditions of the test to compensate for temperature variation and to relate ChE levels to the degree of poisoning.

We thank the Chief Scientist of the Ministry of Supply for permission to publish this paper. We also thank Dr. Donald Hunter, Director for Research in Industrial Medicine, for seconding one of us (J. D. N.) to C.D.E.E., Ministry of Supply, Porton, to facilitate the development of this work.

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Speaking at a largely attended council meeting of the Invalid Children's Aid Association on May 13, Dr. F. S. COOKSEY, director of the department of physical medicine at King's College Hospital, London, described the rehabilitation of the physically handicapped child under three heads: medical care, education of the mind and body, and "settlement," both at home during school life and later at work. With regard to the first, Dr. Cooksey stressed the importance of early diagnosis, particularly in cases of cerebral palsy, and of integrating the medical care under one doctor. "Only one man can integrate the treatment of the child, and he is the family doctor—who frequently does not," said Dr. Cooksey. So far as education is concerned, he thought that too many children with potentially normal brains were suffering from lack of education because they are segregated on account of their physical handicaps. "We should realize that the physically handicapped child should earn its living with its brain, not necessarily with its hands." Craft work was emphasized too much. Speaking of settlement in the home, Dr. Cooksey drew attention to permissive regulations under the National Assistance Act which allow for alterations to be made in the home so that the handicapped child can live more comfortably—such things as the widening of doors, the erection of ramps, and special appliances and furniture.

Medical Memorandum

Female Circumcision and the Age of the Menarche

From previous observations (Ellis, 1950; Wilson and Sutherland, 1953) it is evident that in tropical countries the onset of menstruation may be early or late compared with that for English children, but that it is not determined solely by the climate.

Studies in African ethnopsychiatry (Carothers, 1953) suggest that environmental factors may be of importance in the development of personality and constitution. It is of interest, for example, that exophthalmic goitre (Graves's disease), which may be associated with personality type (Martin and Fisher, 1945), is rare in Africans (Gillman and Gillman, 1951; Carothers, 1953; Davidson, 1954; Wilson, 1954). It is well known, too, that changes in environment which directly or indirectly modify glandular function may affect menstruation in English girls (Browne, 1950).

During nutritional investigations in Sierra Leone which extended from December, 1953, to February, 1954, the opportunity arose to investigate the influence of initiation rites, which include female circumcision, on the age at menarche of Africans. A comparison was made between Creole girls who are Colony-born Africans, among whom no circumcision is practised, and girls belonging to native tribes in the Protectorate, who at the age of about 12–13 years retire into seclusion for ceremonies of initiation. These rites are characterized by an operation on the clitoris and labia minora, which may vary from small incisions to total excision, with the object of restricting sexual pleasure. After this the girl is ready for marriage; without the operation she will not obtain a husband. This initiation and operation usually precedes the menarche; in view of the high emotional content of the ritual it therefore seemed possible that the onset of menstruation might be affected.

Records for the tribal girls were particularly difficult to obtain, and data were available for only 33. The number of Creole girls studied was 129. The present age of each girl was recorded, together with a note whether or not her periods had started. With this information the average age of the menarche and its standard deviation may be calculated, using the statistical technique of probit analysis. The results obtained may be compared with corresponding results for 2,590 girls in the South of England (Wilson and Sutherland, 1953). None of the differences is statistically significant (see Table). Although the number of tribal girls is small, it may be concluded that there is no evidence that the initiation and operation has any substantial effect upon the age of the menarche.

	No. of Girls	Average Age of Menarche (years)	Standard Deviation (years)
Tribes	33	13·44	1·30
Creoles	129	13·65	0·94
S. England	2,590	13·49	1·19

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Reviews

HOWELL'S PHYSIOLOGY

A Textbook of Physiology. Edited by John F. Fulton, M.D., with 12 collaborators. 17th edition. (Pp. 1,275+xlii; illustrated. 94s. 6d.) Philadelphia and London: W. B. Saunders Company. 1955.

The seventeenth edition of what was originally *Howell's Textbook of Physiology* appears under the editorship of Professor Fulton and twelve other distinguished American physiologists; altogether, however, it is the work of thirty contributors. A conscientious review of a book containing over 1,200 pages is neither feasible nor expected by the editor, so I can only express an opinion of its merits based on a cursory glance through the whole and a careful reading of those parts about which I know more than the ordinary run of physiologists.

A general word of praise may be uttered at once: if I were going to teach physiology in some obscure medical school in the heart of Africa, isolated from the modern literature and given the opportunity to take only one book with me, then the textbook under review would be the ineluctable choice. I say this with a strong feeling of disloyalty to an old favourite and the only other large textbook with which a comparison is invited—namely, Starling's *Principles of Human Physiology*; and I say it, furthermore, in spite of the poor literary presentation, the immature judgment, and the obvious lack of any guiding spirit that are revealed by some of the contributions in the book under review. It is unfortunate, but true, that the cause of these defects—the multiple authorship—constitutes the very reason why the book should be the more valuable as an aid to teachers; the author of each section is, or should be, familiar with the literature relevant to his subject-matter, whereas the single author of a large text must, for most of the time he is writing, be dealing with subjects to which, in the course of his everyday activities, he does not normally devote much thought. Scientific writing is not, and should not be, a whole-time task; rather should it be the occupation that fills up idle hours when the day in the laboratory or clinic is over.

Treated in this way, there is an obvious limit to what may be expected of a single author, and it may well be argued that the writing and keeping up to date of a large textbook covering the whole field of physiology are a task beyond the capacities of anyone who is not a complete slave to his work. This consideration, whilst it emphasizes the necessity for multiple authorship, raises the question of the place of large comprehensive textbooks in modern physiology; if the treatments of individual aspects were thorough, up to date, and authoritative, they would occupy a welcome place on the shelves of all research workers and teachers, although their use to medical students—the people for whom they were primarily written by their original authors—would be negligible on account of their size. Unfortunately, an inspection of those parts of Fulton's book on which I feel justified in expressing an opinion reveals that these standards are not always attained; the authors have not always taken the trouble to master the details of the work they describe, and one has the suspicion that they have not always had recourse to the original literature, taking their facts and opinions at second-hand from reviews. (An obvious exception is that part of the book dealing with the nervous system; constituting nearly half the book, it is in itself a scholarly monograph.) Since it fails, therefore, as an introduction to most subjects for the research worker, and since it is unsuitable on account of its size for the medical student, the remaining function—namely, as a source of ready knowledge for teachers in a hurry to prepare a lecture—stands as its sole justification for existence.

The alternative to such a book is a series of monographs covering the whole field of physiology; such a conception has everything to recommend it, and only begs the question of its execution. The difference between hastily throwing together a chapter or two on demand and constructing an exhaustive and well-considered monograph is the difference between a few weeks' and a year's work; moreover, the ability to write, and the inclination to sacrifice the time required for it, are becoming rarer, while the expenses of producing a scientific book are rising rapidly to the point where it will be impossible to publish at a reasonable price books with the limited circulation one must expect for such specialized works. Thus the modern medical and scientific publisher is confronted with a problem which will not resolve itself easily; meanwhile the large textbooks of physiology remain as anachronistic survivals from a day when research was, perhaps, more leisurely; when the scientist did not, as he seems to do to-day, spend his spare time growing vegetables or usurping the functions of a builder and decorator; when the ability to express oneself with ease was one that was taken for granted in most men of science; and, finally, when the medical student was treated as a reasoning human being instead of as a sausage-skin, to be stuffed full of miscellaneous information by over-zealous preclinical departments, competing among themselves to squeeze in the most of their particular brand of knowledge.

HUGH DAVSON.

NEUROSURGERY

Correlative Neurosurgery. By Edgar A. Kahn, Robert C. Bassett, Richard C. Schneider and Elizabeth Caroline Crosby, with eleven other contributors. Foreword by Kenneth G. McKenzie, M.B., F.R.C.S.(C.). (Pp. 413+xv; illustrated. £7.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1955.

Designed as a textbook for the younger neurosurgeon, this volume has been compiled by a number of authors, most of whom were associated with the late Dr. Max Peet. It therefore reflects largely the views of a single school of neurosurgeons. There are excellent opening chapters on the aids to diagnosis of radiology, electroencephalography, and the use of radioactive isotopes, which are clear and up to date. When dealing with the actual intracranial surgery a great amount of fine detail of operative technique is given together with quite admirably clear, simple diagrams, drawings, and photographs. It is perhaps in the finer points of technical detail that the book is at its best.

Many of the chapters dealing purely with surgery are followed by a neuro-anatomical study of the part of the central nervous system concerned. These are a most valuable addition, and are both clear in content and very well and simply illustrated.

All fields of neurosurgery are amply covered in the book, but it would perhaps have been more satisfactory if the actual figures with survival and mortality rates had been given in all the chapters concerned with methods of treatment, for it is highly important to be aware of the exact volume of experience which has been responsible for the views expressed.

The book is superbly produced and well put together, and the standard of the frequent illustrations is very high indeed.

W. MCKISSOCK.

ACUTE POLIOMYELITIS

Treatment of Acute Poliomyelitis. Edited by William A. Spencer, M.D. Second edition. (Pp. 134+xi; illustrated. 27s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1954.

The recent news from the United States of a partially successful vaccine for poliomyelitis must not be allowed to distract attention from the need to improve provision for treatment of the acute disease, and we must always be prepared for severe outbreaks. Some of the American clinics for the treatment of acute poliomyelitis have for many years led the world as regards their methods, and this small book is specially welcome, for it brings to the clinician a wealth of detailed information about treatment techniques

from a first-class U.S. Poliomyelitis Respiratory Centre, and is published in co-operation with the National Foundation of Infantile Paralysis.

The book is presented like the notebook of a student attending a course of lectures, and consists of nearly 90 short sections from 23 authors. These include such subjects as laboratory guides to respiratory management, indications for tracheotomy, body positioning, care of paralysed muscles, and home care for the respiratory patient. Of special interest to the British reader are the sections on machines for assisted coughing, and the astonishing glossopharyngeal breathing by which patients can be taught to force a series of mouthfuls of air into their lungs by a manœuvre of the tongue and throat. Positive-pressure intratracheal breathing has not yet been adopted in the U.S.A., partly perhaps because anaesthetists are not playing much part in the treatment of poliomyelitis, and partly because the technique of having a tracheotomy in a tank respirator has been developed much more than in this country, to provide an efficient method of treating the "combined" case.

W. RITCHIE RUSSELL.

WORK OF THE CASUALTY OFFICER

The Casualty Department. By T. G. Lowden, M.A., B.M., B.Ch., F.R.C.S. (Pp. 278+viii; illustrated. 37s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1955.

Whilst in some hospitals the work of the casualty department is recognized to be of considerable importance, there are still many places where relatively junior men undertake this responsible work without adequate supervision or training. Mr. Lowden's book should be of particular value to the junior casualty officer, and it is likely to prove helpful to more senior people as well.

Starting with a short chapter on sepsis and antibiotics, the author goes on to describe common septic lesions. Primary suture of some septic wounds is recommended, and, although this may be a reasonable proposition in the hands of the discerning and experienced surgeon, some may question the wisdom of such advice in a book of this type. Then follows a long chapter on the septic hand, which is sound and in accordance with modern enlightened opinion. The chapter on soft-tissue wounds with skin loss encourages the casualty officer to think of early skin replacement without stimulating an unnecessarily officious desire to graft all such wounds. There are further useful chapters on burns and on minor non-emergency surgery. The author mentions the simple method of removing a lipoma by cutting into it and separately shelling out the two halves, and it would have been useful had he described that simple method of dealing with a sebaceous cyst by expressing the contents through a small incision and gently withdrawing the cyst wall. The last few chapters, on organization of the casualty department, anaesthesia, disposal of cases, and legal responsibilities, will all prove of value to the casualty officer.

Certain criticisms of this book must be made. The incorrect spelling of Bunnell and Wolfe is of but minor importance. However, much of the book is written in a rather awkward style which does not make for easy reading, and one may hope that the author will give this matter his attention in any future edition of a work which should prove popular in the casualty department.

R. S. MURLEY.

PHYSIOLOGICAL ACOUSTICS

Physiological Acoustics. By Ernest Glen Wever and Merle Lawrence. (Pp. 454; 148 figures. 80s.) Princeton, New Jersey: Princeton University Press. 1954.

With the possible exception of nuclear physics, there have in recent years been greater advances in acoustics than in any other branch of the physical sciences, and in consequence the literature on the subject is vast. Even to the professional physicist acoustics has the reputation of being difficult, while to those doctors whose work demands that they should keep abreast of events in acoustics much of what is written to-day is a closed book, and many must wish that they had paid more attention to physics during the year in which it formed part of their studies.

To-day physiologists, psychologists, and of course otologists need to have a good up-to-date knowledge of the properties of sound, of how it is conducted to and perceived by the ear, how it reaches the conscious level, and finally the physical basis for the various forms of deafness. Dr. Wever and Dr. Lawrence, from Princeton University, have in their book *Physiological Acoustics* provided a contemporary and authoritative account of the mechanism of hearing which is easy to read and above all is interesting. Nothing of importance is left out, and to the scientific worker interested in acoustics, the physiologist, or the otologist this work is likely to become a standard source of reference. To the otologist in particular the book should appeal, for, despite its title, it does contain some interesting physical facts concerning deafness; and there is a chapter devoted to the forms of conductive deafness and to otosclerosis and the fenestration operation. This puts in a simple form the physical reason for the success of the fenestration operation, and indirectly it helps to explain some of the failures. For the research worker there are details of the general layout and management of animal experiments. Perhaps the most attractive feature of the book is the easy style in which it is written, and this, combined with the experience and authority of Dr. Wever, makes it a book which should be read by all interested in acoustics.

TERENCE CAWTHORNE.

MEDICO-HISTORICAL BIBLIOGRAPHY

Garrison and Morton's Medical Bibliography. An Annotated Check-list of Texts Illustrating the History of Medicine. By Leslie T. Morton. 2nd ed. (Pp. 655+xiii. £5 5s.) London: Grafton and Co. 1954.

How ungrateful we all are to those who serve us best! We daily consult dictionaries, year-books, and bibliographies without a thought of the high skill of those who made them and the vast labour that they involve. There should be a form of short prayer for the souls of the compilers of these works to be muttered when we find just what we want—a rarer event than some might think. Certainly Mr. Morton's "mountain of merit" would have reached a good height by now had we all been as grateful to him as we should be.

The history of this admirable book is as follows. In 1912 Fielding H. Garrison, editor of the *Index-Catalogue of the Library of the Surgeon-General's Office,* published at Washington an extract from that great work as a bibliography of the most important contributions to the literature of medicine and the allied sciences. He used it as a scaffolding for his well-known *Introduction to the History of Medicine.* Later he revised the list and published it in the Johns Hopkins *Bulletin of the History of Medicine,* in 1933. After Garrison's death in 1935 Mr. Morton set to work to revise it. He was in a good position to do this as a result of his experience in the libraries of University College, London, and St. Thomas's Hospital Medical School. In 1943 he produced a complete revision, admirably arranged, of Garrison's original plan. This *Medical Bibliography* has ever since been in constant use by teachers and historians of medicine and has become a standard reference work essential to every library, medical or other, of any importance. It has been the constant companion of the reviewer since it first appeared, and he can heartily recommend it as the most efficient and reliable guide to its subject that is known to him. The book has been for some time out of print, and Mr. Morton, now Information Officer of the *British Medical Journal,* has produced a second edition with nearly 7,000 entries as against the 5,500 of the first. For conciseness, convenience, accuracy, and accessibility of its vast store of information the book has no rival. We wish it the success that is its just due.

CHARLES SINGER.

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SATURDAY JUNE 4 1955

SIR HENRY DALE

Sir Henry Dale's eightieth birthday, which falls on June 9, will bring to him messages of good will from throughout the world of medicine and science, and indeed from far beyond it. To those who are familiar with Sir Henry's apparently boundless energy and enthusiasm the fact that such a young man has now completed nearly eighty years of active life will be a matter for admiration and even astonishment. To those who know of him only from his publications, and especially from the classical papers which appeared from his pen in the early years of the present century, it might be surprising that Sir Henry Dale is not already an honoured member of the pantheon of the past. Those who are acquainted with him personally realize that in him exists the living embodiment of a most interesting period of medical history; and history that lives is always entrancing.

But Sir Henry has always been much more than an outstandingly successful investigator. He almost alone now has claim—a claim that he himself would undoubtedly reject—to be a polymath in the world of medical sciences. True, he has had the good fortune to grow in stature during a period of unprecedented expansion in scientific knowledge, and he has himself contributed to the advance of knowledge in so many different aspects of medical science that familiarity with his own publications alone is a liberal education in itself. But nobody can fail to be awed at the range of knowledge he commands. Indeed, nobody can again hope to attain the degree of understanding and experience in every aspect of medical research such as Sir Henry can bring to bear upon any problem before him, whether it be biological standardization, the properties of chemotherapeutic agents, or synaptic transmission of the nerve impulse. As Lord Adrian writes in our opening pages this week, conventional labels fail to apply to Sir Henry, whose achievements can be claimed by anatomists, physiologists, pharmacologists, biochemists, and even, let it be said, by chemists, for he was at one time Fullerian Professor of Chemistry at the Royal Institution, London.

Claude Bernard was described by Professor Charles Singer as "a severe and powerful thinker with an Olympian intellectual aloofness." "Aloofness" is a word that could never be applied to Sir Henry Dale, appropriate though the rest of the quotation may be. Although Sir Henry valued greatly the time he spent in Germany during his early years, and particularly his period in Ehrlich's laboratory, he never became a "Geheimrat." As director of the National Institute for Medical Research and President of the Royal Society during the dark early years of the war, his responsibilities were tremendous, but always he remained a friend as well as a mentor of those colleagues, senior and junior, who had the good fortune to be associated with him. His personal laboratory (F4) at the National Institute, whence came so much of scientific importance between the wars, was not a laboratory alone. F4 was indeed a nursery from which emerged many whose inspiration and accomplishment owe much to a director who continued to work with his own hands for as long as a laboratory was available. His care for and interest in the work of all those who were associated with him was witnessed by the frequency with which Sir Henry's itching pencil clarified and illuminated the many publications which came from the Institute during his tenure of the directorship. The rounded periods—reminiscent both of the Prayer Book and of Gibbon—of his own publications have set a standard of lucidity and precision in scientific writing which has influenced many but which none can equal.

Many years ago the late Sir Frederick Gowland Hopkins wrote: "Up to near the end of the last century nearly every expert looked to the influence of the nervous system alone as concerned with the co-ordination of functions in the body; the conception of chemical regulation and co-ordination had achieved no place in the mind of the majority." How the researches of Sir Henry Dale have resulted in a blending of the idea of chemical regulation and co-ordination with that of the role of the nervous system will be clear from the contributions of Professor J. H. Burn (page 1357), Professor Otto Loewi (page 1356), Dr. Herbert S. Gasser (page 1359), and Lord Adrian (page 1355) in the *Journal* this week. A point that stands out in these accounts is the significance of a mind prepared to evaluate the unexpected and seemingly irrelevant result. The apparently casual use of post-pituitary extract in control experiments which formed part of an investigation concerned with the biological effects of preparations from ergot led surely, in Dale's hands, to the recognition and investigation of the powerful and beneficial oxytocic effects of the posterior pituitary gland. Who would expect that an examination of the pharmacological properties of an extract or ergot could lead also to the

recognition of acetylcholine as a chemical transmitter of nervous impulses, or of histamine as a substance of such wide biological significance as is now recognized? Fortunately Sir Henry Dale was there to appreciate the import of these apparently insignificant initial observations, and to rear thereupon such a structure of knowledge that now each step in the development of it seems to have been inevitable. But it was inevitable only because Sir Henry with his agile and unprejudiced mind was there to seize upon the significance of the apparently irrelevant event. The final demonstration in 1936 that acetylcholine is a transmitter of impulses passing along voluntary motor nerves was the culmination of a series of papers on the subject which stretched over nearly a quarter of a century. From this developed the use of neostigmine in myasthenia gravis and as an antagonist of D-tubocurarine in anaesthesia. The demonstration of humoral transmission in ganglia led naturally to the investigation of the pharmacology of methonium compounds and to the use of a hexamethonium to ensure a bloodless field in surgery. The recognition of the relationship of histamine to anaphylaxis by Dale and Laidlaw in 1919 ultimately resulted in the development of the antihistamine substances which are now of value in many allergic and related conditions. And so the process continued; particular and apparently casual laboratory observations leading to general ideas of significance in medicine as a whole.

Throughout long periods of international distinction and responsibility Sir Henry has been ably supported by his gracious wife, and Lady Dale is known to investigators of all ages throughout the world as a kindly and generous hostess. To Sir Henry and Lady Dale we send our greetings on this most joyous occasion.

PULMONARY OEDEMA

Cardiac asthma and acute pulmonary oedema are commonplace medical emergencies, and it usually falls to the family doctor to treat the distressing attacks of paroxysmal nocturnal dyspnoea which are so alarming to the patient and his relations. Though the bedside diagnosis of pulmonary oedema presents little difficulty, and orthodox treatment is usually successful, the underlying mechanism of the attacks has hitherto been a matter of conjecture and treatment has been largely empirical. In the St. Cyres lecture, published at page 1361 of this issue of the *Journal*, Dr. G. W. Hayward reviews many of the problems of pulmonary oedema in the light of experimental data obtained by modern cardiological technique.

Acute pulmonary oedema occurs most often as a complication of hypertensive heart disease or aortic valvular disorders, but it is also seen not uncommonly in the course of mitral stenosis. It is perhaps not fully appreciated that acute pulmonary oedema may be the only manifestation of acute myocardial infarction, the underlying disease often being overlooked because of the absence of the characteristic substernal pain. The onset of pulmonary oedema depends on changes in the balance between the hydrostatic pressure within the capillaries and the osmotic pressure of the plasma and in the permeability of the capillary walls. An additional factor in patients with chronic venous congestion is that the pathological thickening of the barrier between capillaries and alveoli greatly impedes transudation of fluid into the alveoli. Studies of the pressures in the pulmonary circulation by means of cardiac catheterization confirm that pulmonary oedema occurs only when the pulmonary capillary pressure is greater than the effective plasma osmotic pressure. In the early stages this gives rise to interstitial oedema of the lung, and Hayward believes that a similar state probably exists in a more chronic form in patients with congestive heart failure, when it is responsible for the dyspnoea of cardiac failure by preventing normal lung distension. In acute pulmonary oedema the interstitial fluid is at first removed by the lymphatics, but eventually the fluid breaks through the barrier into the alveoli, and there is a sudden flooding of the respiratory tract. At some stage in this process the additional factor of increased capillary permeability also helps to cause oedema, and it may be that this is the additional impetus enabling the oedema fluid to break through into the alveoli. It is not certain what leads to the increased capillary permeability: in the late phases of pulmonary oedema it is probably aggravated by anoxia, but at the beginning of the attacks anoxia is not severe enough to have this effect, and it is possible that there is a neurogenic cause for the early increase in permeability. The clinician is aware that many attacks of acute pulmonary oedema seem to be aggravated by emotion, by unusual exertion, and by infection, and it now appears that all these factors exert their deleterious effect by increasing the pulmonary capillary pressure. The attacks, which so often occur in the early hours of the morning, are caused by an increase in pulmonary congestion when the orthopnoeic patient slips down in the bed, or by a sudden increase in venous return to the heart when a sudden muscular movement takes place during sleep.

Recent studies have thrown no new light on the treatment of acute pulmonary oedema, but they have confirmed the soundness of traditional therapy and

supplied a logical explanation for many forms of treatment already known to be effective. Any measure diminishing either the venous return to the heart or the pulmonary capillary pressure can relieve the attack in the early stages before capillary damage from anoxia has taken place. In this way venesection and administration of aminophylline exert their good effect. Morphine has long been a stand-by in the treatment of pulmonary oedema, and although there is no direct proof of its mode of action it probably lowers capillary pressure by allaying anxiety. It may also act by depressing muscle tone and thus diminishing venous return to the heart, and at the same time the cardiac output falls, since metabolism is lowered. The use of digitalis requires some caution. There can be no doubt of the value of digitalis in the treatment of hypertensive heart failure, but the intravenous use of digoxin has been known to precipitate acute left ventricular failure by its vasopressor effect. In patients with mitral stenosis, attacks of pulmonary oedema usually disappear altogether after the operation of mitral valvotomy. It remains important to treat chronic venous congestion between the attacks of pulmonary oedema by digitalis, by the mercurial diuretics, and by limiting the intake of salt. It is remarkable how effective these simple measures are in delaying, or even in preventing, further attacks of acute pulmonary oedema.

TRIETHYLENE-MELAMINE

Three years ago we discussed in these columns[1] attempts to find substitutes for nitrogen mustard in the treatment of Hodgkin's disease, lymphomas, and chronic leukaemias. Nitrogen mustard itself has serious disadvantages. It must be given intravenously, and it often causes severe nausea and vomiting; even when every care is taken the veins tend to become thrombosed; some degree of bone-marrow depression is almost always produced and is occasionally a danger to life. Triethylene-melamine at first seemed a promising substitute, for it could be given by mouth, and gastro-intestinal upset was less severe and less frequent. Early clinical trials[2–7] showed that its therapeutic effects were similar to those of nitrogen mustard and it was thought to be more useful in the chronic leukaemias. Now from further experience it has become clear that triethylene-melamine has grave drawbacks. In cases of generalized Hodgkin's disease quite striking remissions may be obtained with it, but it is difficult to predict in advance which patients will respond. E. K. Blackburn and G. M. King[8] state that complete therapeutic failures are less frequent than with nitrogen mustard, but M. M. Wintrobe *et al.*[9] prefer to administer nitrogen mustard first and use triethylene-melamine only for maintenance therapy. L. M. Meyer *et al.*[10] thought the results were inferior to those obtained with nitrogen mustard. On the other hand, most workers find that in chronic lymphatic leukaemia much better control is possible with triethylene-melamine. Patients are extremely sensitive to the drug and a single dose of 2.5 mg. may have a significant effect.[9] Blackburn and King consider that triethylene-melamine is probably the treatment of choice in many cases of chronic lymphatic leukaemia. However, this malady is often symptomless for many years even when generalized lymph-node enlargement, high lymphocyte counts, and heavy infiltration of the bone marrow are present. There is no satisfactory evidence that treatment of such patients defers the onset of symptoms or increases the expectation of life. Symptoms resulting from a group of large nodes are probably better treated by local radiotherapy than by chemotherapy, and once anaemia or thrombocytopenia supervenes none of the chemotherapeutic agents available are of any significant value.[9] Triethylene-melamine has given benefit in cases of chronic myeloid leukaemia; much larger doses are required than in the lymphatic variety, and although good remissions can be induced they are difficult to maintain.[6 10 11] "Myleran" (1-4, dimethanesulphonyloxybutane) appears to be far more effective in this condition,[9] particularly in maintenance therapy, but administration of it is probably better postponed until radiotherapy has lost its effect. However, it may be justifiable to give myleran first if *x*-ray facilities are not available.[12]

The greatest danger of triethylene-melamine is its extreme toxicity to the bone marrow—its narrow margin of safety and the "unpredictable vulnerability of the marrow."[10] Even with the most scrupulous precautions irreversible damage of the bone marrow may follow treatment. The doses recommended in almost all of the earlier reports have since proved to be far too high, and, because of fatalities after doses well within the therapeutic range, all investigators have become extremely cautious. Deaths have been recorded following total doses as small as 10 mg.[10] and 7.5 mg. (0.124 mg. per kg. body weight).[8] Furthermore, patients who have received two or three courses of treatment without experiencing depression of bone marrow have sometimes succumbed to a subsequent course.[13 14]

The capricious behaviour of triethylene-melamine is explained by its chemistry. The molecules tend to polymerize, with resulting loss of activity. Samples thus vary in potency, and P. Alexander and W. C. J. Ross have shown wide variation in laboratory tests which include hydrolysis rates, capacity to combine with desoxyribonucleic acid, and ability to gelate soluble proteins. It

1 *British Medical Journal*, 1952, **1**, 1343.
2 Karnofsky, D. A., *et al.*, *Arch. intern. Med.*, 1951, **87**, 477.
3 Paterson, E., and Boland, J., *Brit. J. Cancer*, 1951, **5**, 28.
4 Hansen, P. B., and Bichel, J., *Acta radiol. (Stockh.)*, 1951, **36**, 469.
5 Bayrd, E. D., *et al.*, *Cancer*, 1952, **5**, 336.
6 Silverberg, J. H., and Dameshek, W., *J. Amer. med. Ass.*, 1952, **148**, 1015.
7 Rundles, R. W., and Barton, W. B., *Blood*, 1952, **7**, 483.
8 Blackburn, E. K., and King, G. M., *J. Fac. Radiol.*, 1954, **6**, 96.
9 Wintrobe, M. M., *et al.*, *Ann. intern. Med.*, 1954, **41**, 447.
10 Meyer, L. M., *et al.*, *Acta med. scand.*, 1952, **144**, Suppl. 272.
11 Bond, W. H., *et al.*, *Arch. intern. Med.*, 1953, **91**, 602.
12 Galton, D. A. G., and Till, M., *Lancet*, 1955, **1**, 425.
13 Haddow, A., *Proc. roy. Soc. Med.*, 1953, **46**, 692.
14 Nabarro, J. D. N., ibid., 1953, **46**, 696.
15 Sparks, S. J., *et al.*, *Cancer Res.*, 1954, **14**, 753.
16 Everett, J. L., *et al.*, *J. chem. Soc.*, 1953, 2386.
17 Haddow, A., *Ciba Foundation Symposium on Leukaemia*, 1954, London.

is most unsatisfactory for clinicians to have to depend on so unstable and toxic a compound. Yet no satisfactory substitute is available, though many substances are undergoing clinical trials, especially in the United States. "Thio-tepa" (triethylene-thiophosphoramide), closely allied to triethylene-melamine but chemically less reactive, has been very effective in an experimental leukaemia[15]; but clinical trials are still at an early stage, and some workers have found it less beneficial than triethylene melamine.[9] W. C. J. Ross and his colleagues[16] have synthesized a series of water-soluble aromatic nitrogen mustards which are powerful inhibitors of the transplanted Walker rat tumour. One of these, known as "CB1348" (di-2-chloroethyl-*p*-amino-phenylbutyric acid), has been tried clinically; preliminary results have shown that the drug may be effective in Hodgkin's disease, lymphosarcoma, and lymphatic leukaemia.[17] CB1348 is given orally, is said to be free of side effects, and unlikely to produce irreversible damage to the bone marrow unless large doses are given. But toxic substances of this class cannot do more than palliate, and a solution of the problem of radical therapy in this distressing group of diseases certainly lies elsewhere.

SWELLINGS OF THE SALIVARY GLANDS

Recurrent swelling of a salivary gland is a familiar clinical problem, but except when calculi are present the aetiology of the condition is often obscure and treatment difficult. This is particularly true of the parotid, where stone formation is uncommon and recurrent parotitis is more often seen. In a recent Hunterian Lecture S. S. Rose has reported his findings in 192 cases of recurrent swelling of the parotid and submandibular salivary glands.[1] Careful radiological examination of these patients, including sialography, has done much to clarify the aetiology of the condition. In this series of patients, 74 had recurrent swelling of the submandibular gland, and in only two of these was the obstruction of the duct not due to a stone. Rose has produced a satisfactory classification for the causes of recurrent parotitis. Among the 118 patients in his group, duct obstruction accounted for 42 and recurrent infection for 66. Less common causes included congenital dilatation of the ducts of the gland and Sjögren's syndrome. Calculi were present in less than 3% of patients with swelling of the parotid.

Obstruction of the parotid duct is usually near its orifice at the papilla. In young adults the obstruction occurs about the time of eruption of the third molar tooth. It is believed that the papilla becomes damaged as a result of alteration in the mechanism of mastication. In patients over the age of 40 the papilla may be damaged by an ill-fitting denture. Recurrent pyogenic parotitis is usually related to inhibition of the normal secretion of saliva, which is decreased or sometimes absent, and may be associated with xerostomia.

Treatment of recurrent parotitis depends in the first instance on an accurate diagnosis, and here sialography is a helpful investigation. Duct obstruction is treated by removal of the underlying cause, such as an ill-fitting denture, and dilatation of Stensen's duct with a lacrimal dilator. Often one dilatation is sufficient to cure the condition. In cases of recurrent infection general treatment is directed towards the correction of anaemia, achlorhydria, and oral sepsis. Patients are advised not to eat dry food, and chewing-gum is beneficial to patients with xerostomia. Infection is treated by injecting 1 g. of streptomycin in 2 ml. of solution into the duct daily for six days. This injection acts not only because of its antibiotic effect but also by mechanically dilating and washing out the duct.

[1] Rose, S. S., *Ann. roy. Coll. Surg. Engl.*, 1954, **15**, 374.

INTERNATIONAL NON-PROPRIETARY NAMES

About five years ago a Subcommittee on Non-proprietary Names, attached to the Expert Committee on the International Pharmacopoeia, was appointed by the World Health Organization, and its sixth report was recently issued. The purpose of the subcommittee was the establishment of an international system of common nomenclature for new pharmaceutical products comparable to the activity in the national field of the British Pharmacopoeia Commission for the last fifteen years and to the American Medical Association for a longer period. Since 1950 the Scandinavian Pharmacopoeia Council has issued lists of non-proprietary names known as N.F.N. names (Nordisk Farmakopenaevn). The World Health Organization invited national pharmacopoeia commissions, drug manufacturers, and others to report on drugs for which international non-proprietary names were required and to suggest names for them. The subcommittee of three members were required to deal with the proposals by correspondence, and the chairman, Professor R. Hazard, of Paris, after consultation with his colleagues, was to decide on the names. The international non-proprietary names so selected were sent to pharmacopoeia commissions and other interested bodies with a recommendation that they be adopted and protected from registration as trade marks. Early in 1951 a first short list of names was issued, and a second list appeared towards the end of the year; few of the names were novel, most being already well established in national pharmacopoeias or works of reference.

By the end of 1952 a total of 430 names had been issued, many of them newly coined, but about this time very strong criticisms were made, especially in the United States, of the procedure used for the selection and publication of the names. This led to the issue by the Executive Board of the World Health Organization of a new procedure and a list of guiding prineiples to be followed by its subcommittee. In effect, all names previously issued were withdrawn and a three-stage process for publication was applied. Names proposed are first considered by the subcommittee, and, if acceptable within the "guiding principles," then published in the *Chronicle of the World Health Organization* as "proposed international non-proprietary names." During the six months after publication any interested person may raise formal objection to a proposed name,

and, in so far as objection is sustained, the name must be withdrawn by the World Health Organization. If no objections remain at the end of six months the name is then issued as a "recommended international non-proprietary name." By these means legitimate interests in private property in names are safeguarded, but there can be no prospect of meeting the essential need for a reasonably quick decision on a new name. The period of six months allowed for formal objection was recently reduced to four months, but although a list of "proposed" names was published in October, 1953, none attained the status of "recommended" names until the end of April, 1955.

The difficulties in the way of agreement at the international level are no doubt immense, but it can scarcely be possible for the national bodies responsible for the issue of non-proprietary names to withhold decisions for 18 months or more until "recommended" names are available from Geneva. To achieve its objective, the World Health Organization will need to provide the facilities for quicker decisions. Failing this, the subcommittee may come to function only in a general advisory capacity and as a clearing-house of information on national drug-naming activities.

TRYPSIN IN THROMBO-EMBOLIC DISEASE

For many years the proteolytic enzyme trypsin has been of interest to people studying blood coagulation. Its *in vitro* properties in promoting clotting were the first to be investigated. Ferguson and Erickson[1] showed that the addition of trypsin and calcium to plasma caused clotting in 16 seconds; after the addition of calcium alone the plasma took 95 seconds to coagulate. Whether it can be concluded from this that proteolysis plays a part in physiological blood coagulation is not known. It is perhaps significant that inhibitors of trypsin, such as soya-bean trypsin inhibitor, also oppose coagulation. In recent times it is not so much the coagulant properties of trypsin which have been of interest, but rather its action as an agent for the destruction of fibrin; such dissolution of fibrin is referred to as fibrinolysis. I. Innerfield and his co-workers[2 3] and M. E. Peck[4] have reported on the therapeutic trial in man of trypsin preparations for intravenous and intramuscular administration. The object of therapy with heparin and drugs of the coumarin group is to stop the spread of intravascular clotting; in contrast, trypsin is intended to remove intravascular thrombus when it has formed.

Our knowledge of human fibrinolysis is incomplete, but *in vitro* activation of proteolytic enzyme systems in plasma capable of destroying fibrin has been produced by various methods. The active enzyme is called plasmin, and it is believed to have a precursor plasminogen. Plasminogen can become plasmin *in vitro* under the influence of culture filtrates of *Streptococcus haemolyticus* (streptokinase).[5] The system can be activated also by certain inorganic solvents such as chloroform or ether, which possibly remove inhibitors.[5] It is thought that trypsin activates plasminogen to plasmin,[6] and that it may in addition have a direct action on fibrin itself.[5] Innerfield *et al.*[5] have studied the effect of intravenous administration of trypsin on experimentally produced thrombi in rabbits and dogs. They have described evidence suggesting restoration of circulation with diminution and even disappearance of thrombus. Microscopical examination showed removal of fibrin with the enclosed cellular and platelet masses without damage to the vessel wall. The same workers did not confirm previous observations of intravascular clotting after injection of trypsin intravenously. Such intravascular clotting is to be expected in view of the readily demonstrable *in vitro* coagulant action of trypsin. They attribute this failure of trypsin to produce coagulation *in vivo* to circulating antitryptic substances; it was not due to significant reduction of clotting proteins by proteolysis, which occurred only after very large intravenous doses of trypsin. Such large doses, therefore, had an anticoagulant activity. The object of trypsin therapy was to administer sufficient to lyse fibrin without unduly affecting the coagulation mechanism. Since carrying out these animal investigations Innerfield *et al.*[2] and Peck[4] have reported the use of trypsin in man. They report favourably on the results of administering intravenous trypsin for thrombophlebitis. As an incidental finding during these observations, they noticed that trypsin had an apparently dramatic effect on inflammatory processes quite apart from its action on intravascular thrombus. Minor general reactions were not uncommon after intravenous administration of trypsin. They included immediate flushing of the face, a general feeling of warmth, and occasionally a sense of suffocation. Sometimes a delayed reaction appeared some hours after the injection, with nausea, vomiting, and abdominal pain. At the site of intravenous injection a local phlebitis was occasionally found. More recently Innerfield[3] has reported on the favourable effect of intramuscular trypsin on the prevention of relapse in cases of chronic recurrent thrombophlebitis.

The assessment of any therapeutic agent in thrombo-embolic disease is difficult, and the results of further trials are awaited with interest. It can be shown *in vitro* that fibrinolytic activity is most successful when the enzyme is given optimal opportunity for contact with the fibrin. In a completely occluded vessel the greater part of the thrombus will be beyond the reach of administered trypsin. The work, however, is important in that it represents a renewed interest in the dissolution of fibrin rather than the prevention of its formation by anticoagulant drugs.

We record with regret the death on May 28 of Dr. C. W. Buckley, the distinguished rheumatologist, at the age of 80. He was formerly consulting physician to the Devonshire Royal Hospital, Buxton, and editor of *Annals of the Rheumatic Diseases*.

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[1] Ferguson, J. H., and Erickson, B. N., *Amer. J. Physiol.*, 1939, **126**, 661.
[2] Innerfield, I., *et al.*, *J. Amer. med. Ass.*, 1953, **152**, 597.
[3] —— ibid., 1954, **156**, 1056.
[4] Peck, M. E., ibid., 1954, **154**, 1260.
[5] Innerfield, I., *et al.*, *J. clin. Invest.*, 1952, **31**, 1049.
[6] Kocholaty, W., *et al.*, *Blood*, 1952, **7**, 882.

EMERGENCIES IN GENERAL PRACTICE

ACUTE HEPATIC FAILURE

BY

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"Wandering and uncertain shiverings . . . follows a most fatal putrefaction of that noble entrail."
—BOERHAAVE (1742).

Failure of liver-cell function may occur suddenly with deep coma, or its onset may be insidious and associated with a perplexing combination of mental and neurological signs. In either category its early recognition is important because it is often reversible and its recurrence can be anticipated and prevented.

The features common to all forms of acute hepatic failure are cerebral changes, fetor hepaticus, and mild fever.

The cerebral changes are diffuse, and all parts of the central nervous system may be involved. Mental disturbances are the most conspicuous; change in personality, confusion, mania, and sometimes screaming are followed by stupor and eventually coma ("hepatic coma") resembling a deep sleep. Disordered motor activity is shown by the "flapping" tremor reminiscent of the beating of a bird's wings. When the patient holds his arms in front of him with his fingers separated, rapid irregular movements occur in bursts, with flexion extension of the wrists and metacarpo-phalangeal joints. There is also a fine 6–9-per-second tremor of the outstretched hands. The movements disappear in repose and are apt to be overlooked if the patient is observed only at rest and not asked to hold his hands in front of him.

Fetor hepaticus is a sweet, slightly faecal odour detected in the breath. It has been likened to the smell of mice or to a freshly opened corpse. It is of intestinal origin.

The temperature may be raised to 100–101° F. (37.8–38.3° C.).

The two commonest causes of acute hepatic failure are acute virus hepatitis and portal cirrhosis of the liver.

Virus Hepatitis

Of the patients with virus hepatitis, 99.8% recover uneventfully. The unfortunate complication of severe liver-cell necrosis is therefore rare and correspondingly difficult to recognize.

In the jaundiced patient mental disturbance provides the earliest warning of this grave turn of events. The patient becomes disorientated, confused, and rambling. Fetor hepaticus and the flapping tremor are present. Jaundice is deep, and persistent vomiting is a bad sign. The temperature rises. Daily percussion of hepatic dullness reveals shrinking of the liver under the right costal margin. Ascites may be present if the illness is of longer than two to three weeks' duration.

Acute hepatic failure can also occur early in the course of virus hepatitis, and is then extremely difficult to diagnose, for jaundice is inconspicuous or absent. The predominant clinical features are mental, and the patient may be admitted to a mental hospital without the hepatic disease being recognized. Helpful diagnostic points are a history of epidemic jaundice in the community or recent injection therapy giving the opportunity for transmission of the hepatitis virus. There is anorexia, the liver edge is tender, and percussion over the right lower ribs posteriorly causes sickening right upper quadrant abdominal pain. The urine contains bilirubin, but sensitive tests may be needed to demonstrate it. Fouchet's method or the new tablet test are equally satisfactory.

Portal Cirrhosis

When hepatic failure complicates chronic portal cirrhosis it is important to know why it has developed. An effort must be made to determine any factor which has depressed the liver function. Gastro-intestinal haemorrhage may have occurred from oesophageal varices, and evidence of haemorrhage must be sought. The bleeding is often slow and occult, and melaena may be detected only by rectal examination. Acute infections such as pneumonia, minor surgical operations such as paracentesis abdominis, and acute alcoholism are other possible precipitants.

When mental or neurological changes complicate well-documented cases of portal cirrhosis, the problem of recognition of the syndrome should not be difficult. Episodes of confusion, flapping tremor of the hands or arms, fetor hepaticus, or stupor can be detected by careful examination. Indeed, if the portal cirrhosis is well recognized, it is difficult to know what else could cause this strange, episodic, neurological picture. Difficulty in diagnosis arises when cirrhosis has not been considered as the underlying cause and the patient is believed to be suffering from one of the other organic dementias, arising from conditions such as cerebral atherosclerosis, cardiac failure, uraemia, Parkinsonism, and disseminated sclerosis, or from the abuse of drugs. The recognition of the underlying cirrhosis, therefore, becomes the key to the diagnostic problem. A history of alcoholism or previous jaundice should be sought, and clinical features of cirrhosis such as mild jaundice, spider naevi on the skin, palmar erythema, ascites, distended abdominal wall veins, and enlargement of liver and spleen noted.

Rarely, the neurological changes in the cirrhotic patient are chronic, and episodes of tremor, confusion, stupor, and coma may occur for years before the correct diagnosis is made. This concept of "chronic intermittent hepatic coma" has been recognized only recently. In the intervals between the episodes the patient is almost normal. Deterioration can often be related to increased amounts of nitrogen-containing substances in the intestines and may therefore follow medication with ammonium chloride, methionine or other amino-acids, or even a high protein diet. The relationship of this observation to the treatment of patients with liver disease is discussed later.

Other Causes

When acute hepatic failure occurs in pregnancy the commonest causes are virus hepatitis and eclampsia. Virus hepatitis of serum type is common in pregnancy because of the many injections performed during antenatal supervision. Cirrhosis is an unlikely diagnosis because patients with chronic liver disease are usually infertile.

Certain poisons cause acute hepatic failure, and suicidal or accidental ingestion of such chemicals as carbon tetrachloride or phosphorus must always be considered.

Prognosis

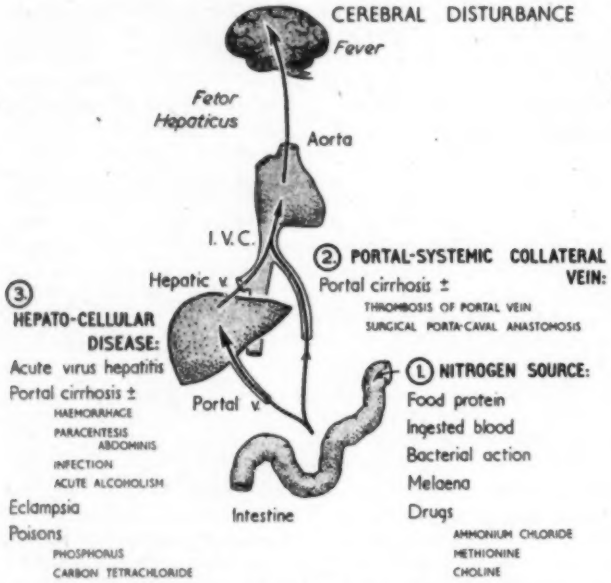
Acute hepatic failure complicating virus hepatitis has a worse outlook than that complicating cirrhosis of the liver. The mortality rate in patients with virus hepatitis and hepatic coma is about 70%. However, the liver possesses such an enormous power of regeneration that even the deeply comatose patient may resume consciousness and ultimately recover completely, with apparently no residual liver damage or shortened expectancy of life. In speaking to the relatives a reasonably hopeful attitude must therefore always be maintained.

The prognosis for acute hepatic failure complicating cirrhosis is very variable and hence difficult to predict. When there has been a clear precipitating factor such as alcoholism or infection the outlook is fairly good because such features can be corrected. When the acute failure follows haemorrhage the prognosis is poor, for the bleeding may be difficult to control.

Insidiously developing hepatic failure in the cirrhotic patient carries a reasonably good prognosis, especially if the patient is not jaundiced and neurological changes can be related to increased amounts of nitrogen in the intestines. With correct dietary management the patients can be maintained in mental equilibrium for years.

Pathogenesis of Acute Liver Failure

All the clinical features of acute hepatic failure are probably due to absorption into the blood stream of intestinal contents which have not been detoxicated by the liver (see diagram). Normally, the liver acts as a useful intermediary



The mechanism of neurological changes leading to hepatic coma (modified from Sherlock, Summerskill, White, and Phear, 1954, *Lancet*, **2**, 453). The three important factors are: (1) Nitrogenous substances in the intestines. (2) Portal-systemic collateral veins diverting blood past the liver. (3) Depressed hepato-cellular function.

filter, which prevents gastro-intestinal poisons reaching the systemic circulation and the brain. The failing liver of hepatitis or cirrhosis is unable to fulfil this function adequately and the by-pass may even be accentuated by the presence of collateral vessels connecting the portal and systemic circulations, as in cirrhosis with portal hypertension. If the portal vein is thrombosed, a not uncommon complication of hepatic cirrhosis, the whole portal blood flow is deviated through collateral channels. Poisons which are apt to gain entrance to the general circulation include bacteria causing pyrexia, various intestinal toxins producing fetor hepaticus, and certain nitrogenous substances causing cerebral disturbance. The actual cerebral poisons present in portal venous blood are unknown, but undesirable effects may follow such nitrogen-containing substances as a high-protein diet, ammonium chloride, urea, methionine, or choline. The portal vein and cerebrospinal fluid contain a high concentration of ammonia in hepatic coma. However, the relation between the neurological changes in man and blood "ammonium" concentration is not close enough to assume that ammonia toxicity is the cause. The patients are not hypoglycaemic and no other constant biochemical abnormality has been demonstrated.

This theory of "auto-intoxication" or *portal-systemic encephalopathy* may appear to be an old one, but it certainly accounts for many of the clinical features which commonly occur in hepatic failure, and it suggests a regime of management which has proved satisfactory in these patients.

Treatment

There is little active treatment that can be undertaken before hospital admission. Therefore admission is urgent and should be arranged as soon as the diagnosis is made. It is important to resist the use of drugs which are detoxicated by the liver, because their prolonged and undesirable action may contribute to the coma. Such drugs include morphine and most barbiturates. If the patient is restless and sedation is indicated, paraldehyde may be given per rectum in a dose of 16–20 ml. emulsified in 60 ml. of normal saline. Otherwise, glucose drinks will suffice as a temporary measure.

The management of the patient in hospital is here given only in outline. The initial care should always be undertaken in an establishment where constant supervision, a suitable dietary regime, and clinical and biochemical assessment of liver-cell function are all available. The basic principles, however, apply equally when the cirrhotic patient is discharged home to the practitioner's supervision.

Treatment in hospital is directed along two lines: (1) eliminating potentially toxic nitrogenous substances from the intestines; and (2) improving hepato-cellular function.

Elimination of Intestinal Intoxicants

Possible toxic nitrogenous compounds include a high-protein diet, methionine, choline, and ammonium chloride, and these are all avoided. The physician is torn between the policy of a liberal protein diet as a general principle in liver disease and the avoidance of protein because of its potential toxicity. When the patient is first observed, protein should not be given, but he should be maintained for one week on glucose and a little fat. This alone may produce a striking remission of the neurological sequelae and permit more adequate assessment of liver-cell function. Such a protein-free diet can be used only temporarily until symptoms are brought under control; thereafter, protein must be gradually increased. A diet containing 25 g. of protein is introduced for one week, and this should be raised by 25 g. during successive weeks. It is usually found that patients with cirrhosis and chronic neurological complications can tolerate only 50 g. of protein daily. It must not be thought that all patients with cirrhosis of the liver should have such a low-protein diet; it is recommended only for those with neurological complications.

During the initial protein-free period, adequate calorific intake must be maintained, otherwise endogenous protein breakdown produces amino-acids and a further metabolic strain on the liver. So long as the patient remains cooperative 2,000 calories can be administered daily by mouth in the form of 20% glucose in fruit juices. Should he be uncooperative, it may be necessary to resort to gastric tube-feeding or intravenous infusions. An intragastric tube supplying 20% glucose in water at a rate of 20–30 drops a minute provides 2 litres or 1,600 calories during 24 hours; 1 g. of potassium chloride is added to each litre.

Intravenous feeding is recommended if persistent vomiting or uncooperation makes the intragastric drip method impracticable. In order to provide sufficient calories without

fluid overload, 20% glucose in water is employed, 2 litres a day being given. Since this would irritate small veins, with a resulting phlebitis, it is delivered into a large venous channel, such as the innominate vein or superior vena cava, by means of "polythene" tubing. This method ensures continuous intravenous feeding for several days.

Since toxaemia from the effect of intestinal bacteria on nitrogen-containing substances may play a part in the genesis of these changes, temporary sterilization of the gut is worthwhile. It is best to choose a broad-spectrum antibiotic such as chlortetracycline or tetracycline, giving 0.5 g. six-hourly orally, or if necessary by stomach tube, as long as the coma lasts or to a maximum of one week. Parenteral antibiotics are not effective.

After an enema initially, daily motions should be ensured with magnesium sulphate.

Improvement of Hepato-cellular Function

This implies the energetic treatment of any factor which is depressing liver function and precipitating failure. Infection is treated with antibiotics, anaemia is controlled by blood transfusion, and alcohol is forbidden. A carbohydrate diet allows the maximal metabolic rest to the liver.

Intravenous glutamic acid has been advocated for the treatment of patients with hepatic coma. Wide experience of it in many parts of the world has failed to show any consistent improvement in patients suffering from a condition remarkable for its day-to-day variation.

Results of Treatment

Any treatment advocated for hepato-cellular failure is difficult to assess, for the cause of the syndrome is uncertain and the clinical state so variable from time to time. Using the above conservative regime, I have treated 21 patients with the syndrome of acute hepatic failure due to virus hepatitis or portal cirrhosis. Two of five patients with virus hepatitis and 11 of 16 with portal cirrhosis have survived episodes of coma.

If the patient with acute virus hepatitis survives acute hepatic failure, recovery is usually complete. The cirrhotic patient, however, is liable to recurrences, and the general practitioner must then decide whether readmission to hospital is necessary. Gastro-intestinal haemorrhage, rapidly accumulating ascites, or deep coma are clear indications for immediate admission to hospital. If, on the other hand, the changes described above are recognized early, conservative management can be employed in the home. Improvement can be reasonably expected within 36 hours, and this may avert unnecessary readmission to hospital.

Next article on Emergencies in General Practice.—"Pulmonary Embolism," by Professor R. B. Hunter.

CHILD WELFARE CENTRE

"PROVINCE OF NATAL" WELFARE CENTRE OPENED IN LONDON

The High Commissioner for the Union of South Africa (Mr. G. P. JOOSTE) on May 26 opened the "Province of Natal" Centre for Child Health in London. The centre is a handsome and spacious erection in Guilford Place, on the dividing border between the boroughs of Holborn and St. Pancras, and adjacent to the Hospital for Sick Children, Great Ormond Street. In addition to serving as a welfare centre, it is to house the Institute of Child Health, hitherto located at the hospital, and it seems to have a fair amount of space unallocated and available for future developments. The ground floor is planned for maternity and child welfare work, with a hall for lectures and meetings, a kitchen for demonstrations, and a creche open on certain afternoons a week in which busy mothers may leave their children. The first floor is given over to school health work, and here all the activities of a school health service which are more conveniently carried out at a clinic than in the school itself will proceed. On this or the floor above there are a dental department, an orthoptic clinic, a clinic for minor ailments, an audiology room, and a child guidance centre, where a psychiatrist and psychiatric social worker will be engaged. Elsewhere in the building are two large laboratories and all their accessories. Special attention was drawn to the system of benches cantilevered from the wall and provided with continuous service racks, while each of the under-bench units is independent and removable.

A South African Benefaction

At the opening ceremony Professor ALAN MONCRIEFF, Director of the Institute of Child Health, explained how this new venture had come about. He reminded the company that the University of London Institute of Child Health was founded in 1946, with a generous gift from the Nuffield Foundation to establish a chair in child health and with the warm support of the university authorities on the one hand and the board of management and staff of the Hospital for Sick Children on the other. Investigations then began to be made into where and how a model welfare centre could be established. In 1947 the Mayor of Durban, Mr. Rupert Brown, came to London, and in an interview with Professor Moncrieff said how sorry he was that the National Health Service newly instituted in Britain prevented the people of Natal from helping Great Ormond Street. "I remember gripping my chair hard as I launched into a tactful explanation to him of how the money could still be used—for our model welfare centre." He had a dreadful feeling that he was too late, but fortunately the Mayor was convinced, the South African Gift Committee was communicated with, and before the end of the year a grant of £106,888 had been made. Then ensued a period of planning and architects' conferences. The University had acquired land, a portion of which was available, and the London County Council signified its willingness to pay 90% of the cost of maintenance and all the salaries of medical and nursing staff. A house committee, with representatives of the L.C.C., the two borough councils from whose areas most of the children will be drawn, and the Institute of Child Health, will control general matters of policy, voluntary help, clinic sessions, amenities, and so forth. Professor Moncrieff added that it was a stipulation at the time of the original gift that the name "Province of Natal" should be associated with the centre.

The object was first to give a model service to the children of this part of London, and also as a university centre to undertake teaching and research. Postgraduate doctors and student nurses would come from Great Ormond Street to learn what was going forward, also health visitors, and it was hoped that the L.C.C. would use the centre in the training of their medical and nursing staffs.

The HIGH COMMISSIONER then formally declared the Centre open and unveiled a commemorative plaque. He explained that the financial assistance which came from the people of Natal was from a fund originally called the "Salute to Britain" fund, expressive of the deep feeling of sympathy for the people of Britain in their ordeal during the war. It was difficult to conceive a more fitting manner in which the money could have been used than in the construction of this Centre to alleviate suffering and promote knowledge in the service of children, in whom lay the future of any nation.

The thanks of the London County Council for the facilities provided by the centre were voiced by its chairman, Mr. NORMAN PRITCHARD, and His Excellency was thanked by Lord WAVERLEY, chairman of the governing body of the British Postgraduate Medical Federation.

MEDICAL MEMBERS OF PARLIAMENT

Below are biographical notes of the members of the medical profession who were successful at the General Election held on May 26. Altogether 20 candidates with medical qualifications stood for election.

Dr. R. F. B. Bennett

Dr. R. F. B. Bennett (Conservative, Gosport and Fareham) was born in July, 1911, and was educated at Winchester, New College, Oxford, and St. George's Hospital, London. He qualified in 1937, and graduated B.M., B.Ch. in 1942. During the war he served in the R.N.V.R., and subsequently with the Fleet Air Arm, first in the Western Approaches, where he was twice torpedoed, and then in Tanganyika and Ceylon, completing more than 500 hours' flying as a pilot. Towards the end of the war he was attached to the R.N. Psychiatric Hospital at Knowle. After the war he was a psychiatrist for South Hampshire. Dr. Bennett contested the East Woolwich constituency in the 1945 election. In 1950 he had a majority of 10,584 at Gosport and Fareham, and a similar majority in 1951. He was Parliamentary Private Secretary to the Home Secretary from 1951 to 1954, and to the Minister of Fuel and Power from November, 1954, to this year's General Election. He has been secretary of the Conservative Parliamentary Committees on Air and Civil Aviation since 1951; psychiatrist to the Institute for the Study and Treatment of Delinquency since 1950; and a member of the South-west Metropolitan Regional Hospital Board since 1953. He was a member of the Steering Committee of the Parliamentary and Scientific Committee from 1952 to 1954. He is a member of the Inner Temple, and holds the rank of surgeon lieutenant-commander in the R.N.V.R.

Dr. R. F. B. BENNETT (Conservative) 30,918
Mr. S. J. Surrey (Labour) 18,432

Dr. A. D. D. Broughton

Dr. A. D. D. Broughton (Labour, Batley and Morley) was born on October 18, 1902. He was educated at Rossall School, Cambridge University, and the London Hospital. He qualified in 1929 and graduated M.B., B.Chir. in 1937. He took the D.P.M. in 1936 and the D.P.H. a year later. Dr. Broughton held appointments as casualty officer at Poplar Hospital and as reeeiving-room officer at the London Hospital before returning to Rossall School for a few years as resident medical officer. He entered general practice in Batley in 1932. During the war he served in the Medical Branch of the Royal Air Force. Dr. Broughton was elected a member of the Batley Borough Council in 1946 and held office as vice-chairman of the public health and of the maternity and child welfare committees. He took his seat in Parliament in February, 1949, after winning the Batley and Morley by-election, and was returned with a majority of 9,885 in the 1950 election, and with only a slightly reduced majority in the 1951 election.

Dr. A. D. D. BROUGHTON (Labour) 27,178
Mr. H. Watson (Conservative) 17,970

Mr. J. D. Cronin

Mr. J. D. Cronin (Labour, Loughborough) was born on March 1, 1916, and received his medical education at St. Bartholomew's Hospital, qualifying in 1939. In the following year he graduated M.B., B.S. at London University, and in 1947 he obtained the F.R.C.S. Mr. Cronin is orthopaedic surgeon to the French Hospital and is an adviser on industrial injuries to a number of trade unions. He is examiner in surgery for the General Nursing Council. During the second world war he served from 1942 to 1946 in the R.A.M.C., attaining the rank of captain.

Mr. J. D. CRONIN (Labour) 24,044
Mr. M. V. Argyle (Conservative) 19,781

Mr. Walter Elliot

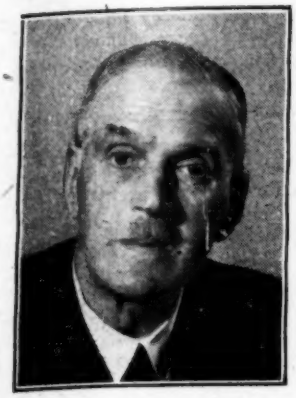
Mr. Walter Elliot (Conservative, Kelvingrove) was born on September 19, 1888, and was educated at Glasgow Academy and the University of Glasgow. He took the B.Sc. in 1910, graduated M.B., Ch.B. in 1913, and proceeded D.Sc. in 1923. The honorary degree of LL.D. has been conferred on him by the Universities of Aberdeen, Edinburgh, Glasgow, and St. Andrews, and Leeds and Manchester, and he is an honorary D.Sc. of the University of South Africa. From 1933 to 1936 he was Lord Rector of Aberdeen University, and he was Rector of Glasgow University from 1947 to 1950. Mr. Elliot was elected F.R.S. in 1935 and F.R.C.P. in 1940. During the war of 1914–18 he served with the R.A.M.C. Mr. Elliot was returned to Parliament as Member for the Lanark division in 1918 and again in 1923, and he was a Member for the Kelvingrove division of Glasgow from 1924 until the General Election of 1945, when he lost his seat by 88 votes to the Labour candidate. In 1946 he was returned to Westminster by the Scottish Universities after a spectacular contest in which all his opponents lost their deposits.

The Representation of the People Act of 1948 abolished the university vote, and Mr. Elliot therefore returned to the Kelvingrove division of Glasgow for the General Election held in 1950, when he had a majority of 1,224, and he was re-elected in the following year with an improved majority. Mr. Elliot became a Privy Councillor in 1932, and from 1923 onwards he held in succession the offices of Under-Secretary of Health for Scotland, Under-Secretary of State for Scotland, Financial Secretary to the Treasury, Minister of Agriculture and Fisheries, Secretary of State for Scotland, and Minister of Health. In 1941–2 he was a director of Public Relations at the War Office.

Mr. WALTER ELLIOT (Conservative) 14,854
Mr. J. L. Williams (Labour) 11,966

Mr. Somerville Hastings

Mr. Somerville Hastings (Labour, Barking) was born on March 4, 1878. He is consulting aural surgeon to the Middlesex Hospital. A student at Middlesex Hospital and University College, London, he graduated M.B., B.S. in 1902 and took the F.R.C.S. in 1904. Mr. Hastings has been interested in medical politics for many years. He was a member of the B.M.A. Planning Commission, whose report was published in 1942. In 1929 he assisted in the formation of the Socialist Medical Association, of which he is a past president. He is also a member of the public health advisory committee of the Labour Party. He was returned as Labour M.P. for Reading in 1923, and again in 1929, and was Parliamentary Private Secretary to the Board of Education in the first Labour Government.

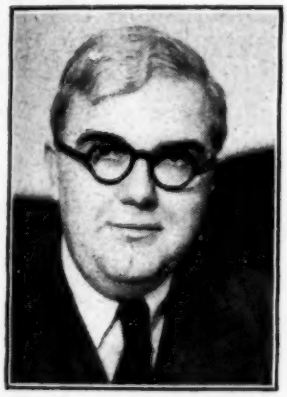


Mr. Hastings has been a member of the London County Council since 1932, and he became chairman of the hospitals and medical services committee of the council in 1934, holding this post for 10 years until he became chairman of the council itself. He was a member of the Curtis Committee, and is now vice-chairman of the children's committee of the London County Council. He is an alderman of the council. At present, at the age of 77, he is a member of the North-east Metropolitan Regional Hospital Board. Mr. Somerville Hastings was returned in 1945 as the Member for Barking with a majority of 18,911; in 1950 with a majority of 20,030; and in 1951 with a still larger majority.

Mr. SOMERVILLE HASTINGS (Labour) 27,129
Mr. B. Massey (Conservative) 12,082

Dr. Charles Hill

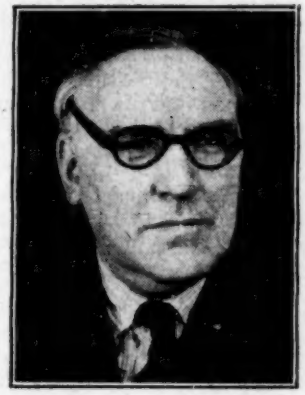
Dr. Charles Hill (Liberal and Conservative, Luton) was born on January 15, 1904, and was educated at St. Olave's School, Trinity College, Cambridge, and at the London Hospital. He qualified in 1927, and graduated M.B., B.Chir. in 1929, proceeding M.D. in 1936. For a time he was a London University extension lecturer, and then spent two years as deputy medical officer of health for Oxford before coming to the B.M.A. as assistant secretary in 1932. Three years later he was made deputy secretary, and in 1944 he became secretary, which post he held until his resignation in 1950. He has been active in the affairs of the World Medical Association, of which body he was president in 1949–50. He was formerly chairman, and is now vice-president, of the Central Council for Health Education. He first stood for Parliament in 1945, when he unsuccessfully contested the Cambridge University constituency as an Independent. In 1950 he was returned for Luton as a Liberal and Conservative with a majority of 1,086, which figure he improved upon at the 1951 General Election. He was Parliamentary Secretary to the Ministry of Food from 1951 to April 7 this year, when he was appointed Postmaster-General, becoming also a Privy Councillor.



Dr. CHARLES HILL (Liberal and Conservative) ... 24,722
Mr. M. Janis (Labour) 20,304
Miss J. Henderson (Liberal) 3,140

Dr. Donald McI. Johnson

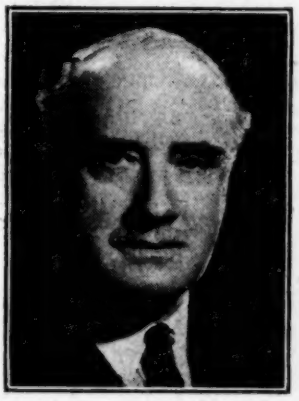
Dr. D. McI. Johnson (Conservative, Carlisle) was born on February 17, 1903. He was educated at Cheltenham College and at Gonville and Caius College, Cambridge, and St. Bartholomew's Hospital, qualifying in 1926. He was in general practice when war broke out in 1939, when, as a Territorial officer, he was mobilized for service in the R.A.M.C. Since the end of the second world war he has founded a publishing firm and has written a number of books. He is a member of Sutton and Cheam Borough Council. He has stood for Parliament on four previous occasions as a Liberal candidate.



Dr. D. McI. JOHNSON (Conservative) 20,071
Mr. A. Hargreaves (Labour) 19,701

Colonel Malcolm Stoddart-Scott

Colonel Malcolm Stoddart-Scott (Conservative, Ripon) was born on September 23, 1901. He was educated at Elmfield College, York, Ashville College, Harrogate, and Leeds University, where he graduated M.B., Ch.B. in 1926, and proceeded M.D. in 1929. Colonel Stoddart-Scott served as D.A.D.M.S. and A.D.M.S. 48th Division in the second world war. He has been honorary secretary of the Conservative Parliamentary Health Committee, and he sat on the Standing Committees which dealt with the National Health Service Bill, Analgesia in Childbirth Bill, Nurses Bill, Milk Designation Bill, and other measures. He was first elected to Parliament in 1945 as the Conservative Member for Pudsey and Otley with a majority of 1,651. In 1950 he was returned for Ripon with a majority of 10,975, and in 1951 he increased his majority to 12,420.



Colonel M. STODDART-SCOTT (Conservative) ... 21,977
Mr. E. Brierley (Labour) 9,912

Dr. Barnet Stross

Dr. Barnet Stross (Labour, Stoke-on-Trent Central) was born on December 25, 1899, and was educated at Leeds Grammar School and at Leeds University. He graduated M.B., Ch.B. in 1925, and was engaged in general practice in Stoke-on-Trent until 1948. Dr. Stross was elected councillor of the City of Stoke-on-Trent in 1937, and in the following year he accepted an invitation to stand as Parliamentary candidate for the Hanley division of Stoke-on-Trent. In 1945 he entered Parliament, representing this division. Dr. Stross served on the Standing Committees responsible for con-

sidering the National Health Service Bill, the Nationalization of Coal Bill, and the Criminal Justice Bill. He was returned as the Member for Stoke-on-Trent (Hanley) in 1945 with a majority of 11,602; for Stoke-on-Trent Central in 1950 with a majority of 16,547; and in 1951, again for Stoke-on-Trent Central, with a slightly reduced majority.

Dr. BARNET STROSS (Labour) 28,452
Mr. G. B. Price (Conservative) 16,097

Dr. Edith Summerskill

Dr. Edith Summerskill (Labour, Warrington), who was born in 1901, was a student of King's College, London, and Charing Cross Hospital. She qualified in 1924. She served on the Middlesex County Council from 1932 to 1938, fought a Parliamentary by-election in Putney in 1934 (reducing the majority against Labour from 22,000 to 2,000), contested Bury at the 1935 General Election, and was returned in 1938 as the Member for West Fulham. In 1945 she was again returned by West Fulham, and was Parliamentary Secretary at the Ministry of Food from then until 1950, when in the next Government she became Minister of National Insurance. In 1946 Dr. Summerskill represented Great Britain at the Food and Agriculture Organization's conference at Washington, and again in 1947 in Geneva. She was one of the organizers of the Socialist Medical Association. In the 1949 New Year Honours List it was announced that Dr. Summerskill had become a Privy Councillor. In 1945 Dr. Summerskill had a majority of 7,521; at the 1950 election she had a majority of 2,849; and in 1951 2,583. She was adopted as the Labour candidate for Warrington at this election in place of Dr. H. B. W. Morgan, the retiring Member, who did not seek re-election.

Dr. EDITH SUMMERSKILL (Labour) 22,721
Mr. H. Davies (Conservative) 17,075

Acknowledgments

The photographs of Dr. Charles Hill and Dr. A. D. D. Broughton are by Elliott and Fry Ltd.; that of Mr. J. D. Cronin by Wakefields of Chiswick; Colonel Malcolm Stoddart-Scott by Bassano; Mr. Walter Elliot by Davis (Streatham); Mr. Somerville Hastings by *Illustrated*; Dr. D. McI. Johnson by *Cumberland News*; Dr. Edith Summerskill by London News Agency; Dr. R. F. Bennett by Barrett; and that of Dr. Barnet Stross was taken privately.

Radiotelephony is being used by many local health authorities in the control of their ambulance fleets, and is to be introduced on a limited scale into the London ambulance service. The health committee of the London County Council proposes to equip six ambulances and a staff car for two-way radio-transmission, and to adapt three more ambulances as reserves, with a control set at headquarters. These ambulances will be used primarily to reinforce general ambulance stations working under pressure; their crews will be able to receive instructions without returning to base, to verify doubtful information quickly, and to report immediately any special circumstances, such as births in ambulances. They will also be a valuable means of controlling operations at any major disaster. The estimated cost of initial equipment is £2,975.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Environmental Cancer Research

SIR,—Sir Ernest Kennaway in a recent article (*Journal*, May 7, p. 1107) called attention to the significance of studying cancer in man from the epidemiological point of view. He emphasizes that this type of cancer research, though it may be empirical, can well lead to the identification of carcinogenic factors for man whose avoidance would be followed by a reduction in incidence of certain cancer types.

For many years Sir Ernest has played a leading role in cancer research, covering many phases of this field. It is thus of interest that of late he has given so much emphasis to the study of cancer as it is influenced by our environment as a practical means of combating cancer. He has pointed out that environmental factors do not only play a role in certain limited occupational fields, but can also affect large segments of the population as, for instance, cancer of the lung and cancer of the cervix. On my visits to London I always look forward to a discussion with Sir Ernest and to learning from him about his latest research in cancer epidemiology. He has contributed greatly to my own interests in this field. This admiration, however, does not prevent us from having occasional differences of opinion.

Sir Ernest believes that the circumcision factor may not account for the low rate of cervical cancer in Jewish women because of the great differences in cervix and penile cancer rates in England, which should both be influenced by smegma application. This view does not consider that differences in tissue susceptibility may account for such variances in rates. Furthermore, there may be co-factors affecting the cervix but not the penis. Similarly, smoking affects both lung and larynx cancer, though here, too, the incidence rates vary greatly.[1] It is important, however, that the incidence pattern be similar among different population groups as far as penile and cervical cancer are concerned for these two types of cancer, as is the case. It is for this reason, added to the statistical evidence available, that we felt the circumcision factor to be consistent with the belief that it aids in lowering the rate of cancer of the cervix.

In respect to the abstinence after menses data, we had no proof that such abstinence was a factor in the low incidence of cervical cancer in Jewish women. Ten out of twenty Jewish women with cancer of the cervix (not five as erroneously stated in the *British Medical Journal* article) did not abstain after menses, whereas five abstained for the full period of seven days.[2,3] We pointed out that these were insufficient cases to allow statistical analysis, though they were in line with the controls. As our other reason as to why we felt that the abstinence period was probably not as important as proposed, we found that the rate of abstinence in Jewish women in New York City in the early fifties, and certainly in the forties and younger age groups, has decreased so markedly that the rate of cervical cancer should have been increasing significantly among Jewish women in this city, a fact which has not been observed. As the younger Jewish women advance into the cancer age, the answer to this question will be even more apparent. Perhaps the abstinence factor could be more easily examined if it could be studied independently from the factor of circumcision. We believe that, since Jews continue circumcision and as long as there are not many inter-racial marriages, the rate of cancer of the cervix will remain low in Jewish women in spite of the fact that they no longer significantly practise the abstinence period. Subsequent years will prove or disprove this concept. We have

repeatedly emphasized, furthermore, that circumcision represents only one of the factors that seems to affect the risk to develop cancer of the cervix. However, in environmental factors, as Sir Ernest has so frequently pointed out, it suffices if we successfully halt exposure to one given factor.

To those who, in addition to carrying out laboratory research, also have the task of caring for cancer patients, the need for preventive measures becomes increasingly clear. Some day it is hoped, of course, that what Sir Ernest calls fundamental research will give us the basic answer and cure for all cancers. However, such an answer and such a cure do not seem within our reach at present. It is therefore important that we must concentrate on the study and modification of environmental factors which seem to influence the development of a majority of our cancers. In this field international co-operation is of first-rate importance. It is along these lines that Sir Ernest Kennaway has made so many significant contributions which have stimulated research in many parts of the world.—I am, etc.,

New York, 21, U.S.A. ERNEST L. WYNDER.

REFERENCES

1 Wynder, E. L., *et al.* "A Study on Environmental Factors of Cancer of the Larynx," in preparation.
2 —— *et al.*, *Amer. J. Obstet. Gynec.*, 1954, **68**, 1016.
3 —— *British Medical Journal*, 1955, **1**, 743.

Measles

SIR,—Dr. J. F. Lund (*Journal*, May 21, p. 1279) raises certain important and urgent principles which require a considerable amount of further thought and attention from all those engaged in the practice of medicine. The subject is the use (and abuse) of antibiotics not only in general practice but also in other branches of medicine.

We seem to be confused over the whole matter. How much of the vast amounts of these drugs, which are now being used and which are costing the nation so much money, are really necessary? It seems impractical and a sign of inexperience that we should immediately think in terms of antibiotics when confronted with all types of infections, irrespective of whether they be severe or slight. We are all agreed that the more severe conditions, such as the pneumonias, meningitis and osteomyelitis, require urgent and adequate treatment with the antibiotics, but is it necessary to treat sore throats indiscriminately with "25 g. of aureomycin, 36 penicillin lozenges and a gargle," as was seen on one prescription handed to a chemist? We seem to have forgotten that these same infections used to settle down without a great deal of trouble, in most instances, a decade or so ago. A further factor which has apparently escaped notice is that it is probable that the virulence of the infecting organisms has altered. There is no question that scarlet fever is now both less frequent and less severe, and that ear infections are also less virulent. Whether this has come about because or in spite of the use of these drugs is a matter for conjecture, discussion, and research. A further question to be answered is: What is the best route for their administration, with special reference to oral penicillin? Are the wide-spectrum antibiotics as necessary as prescribing costs suggest? It may not have been such a bad idea to have retained the restrictions which were previously applied to the use of these drugs in general practice. Another aspect which merits consideration is the steadily rising numbers of fatalities and ill effects attributable to the use of these substances. Yet another thought is to the future. The proportions of resistant organisms are mounting, especially so in the hospitals. It would be disastrous to think that in the future we might run out of antibiotics which would control these resistant organisms.

To return to Dr. Lund's question. In the same measles epidemic, and only some few miles from him, I had in my own practice 135 cases of measles and I did *not* use any prophylactic chemotherapy or antibiotics. Of all these, only four children eventually needed selective treatment with intramuscular penicillin: two catarrhal children who developed an acute chest infection which settled within five days and two other children needed similar therapy for acute otitis media—these also cleared up rapidly with no after-effects. It is most important to know whether these drugs are or are not necessary in view of the almost equally good results with these two differing forms of therapy. We await therefore with great interest and expectation the results of the College of General Practitioners' investigation into this very subject.

To show that antibiotics are not necessary in the vast majority of other common infections in general practice I would like to quote from some figures which I have been keeping over the past few months. I have followed the rule that non-specific therapy be given unless there are definite indications for their administration. The two conditions which have been observed are acute otitis media and acute exudative throat infections. In acute otitis media, out of 80 cases antibiotics (penicillin only was used) were considered necessary in only 39% of cases; there were no complicating after-effects in any of these 80. In the acute sore throats, antibiotics (again intramuscular penicillin was the only one used) were required in only 25% out of the 50 cases seen.

I hope that I have made the issues clear—namely, that we need a reassessment and reorientation in clarifying the indications for the use of antibiotics, especially in reference to their use for minor conditions in general practice.—I am, etc.,

Beckenham, Kent. JOHN FRY.

SIR,—I was interested in Dr. J. F. Lund's letter (*Journal*, May 21, p. 1279) describing his experiences with prophylactic penicillin in measles. Between January and April of this year I treated 100 cases, ranging in age from 5 months to 7 years. They all received an oral penicillin suspension in a dosage of 100,000 units to 200,000 units four-hourly, depending upon age. The only complication I encountered was in the case of a boy aged 3½ years who developed appendicitis seven days after the appearance of his rash. I gather this is a recognized complication of measles, which is a disease primarily affecting the mucous membranes. Incidentally, it was not mentioned as a complication in your interesting leading article on measles in the *Journal* of April 23 (p. 1018).—I am, etc.,

London, S.W.4. G. J. GRAINGER.

SIR,—I would like to endorse Dr. J. F. Lund's remarks in his letter on the prophylactic use of sulphonamides in measles (*Journal*, May 21, p. 1279). I personally have seen just over 80 cases during the recent epidemic with an age range of 6 months to 7 years. In addition there have been about another 100 cases dealt with by the practice. All have had prophylactic sulphonamides and none have developed complications. We may, or may not, have been lucky, but propose to continue with our present routine.—I am, etc.,

Spondon, Derbyshire. R. G. G. TAYLOR.

SIR,—I am afraid Dr. J. F. Lund (*Journal*, May 21, p. 1279) and his principal, Dr. R. G. Wigoder, have drawn false conclusions from a mere coincidence. My partner Dr. T. D. Reilly and I have notified 56 cases of measles since January 1. We have used no prophylactic sulphonamides or penicillin and we have had no case with complications. It is to be hoped that none of the organisms in Dr. Lund's patients will prove resistant to penicillin in later illnesses, otherwise its already expensive use will require increased expense in the use of newer antibiotics.—I am, etc.,

Liverpool, 22. F. R. CRADDOCK.

Disseminated Sclerosis

SIR,—We feel that Dr. Hugh Garland did not do full justice to the book by Drs. Douglas McAlpine, Nigel D. Compston, and Charles E. Lumsden on *Multiple Sclerosis* in the review in the *Journal* of May 14 (p. 1197). It is a valuable book, the first of its kind in this country on this important subject. We calculate that there is approximately one case of disseminated sclerosis per thousand of the adult

population in Northern Ireland, which emphasizes how common is the disease. Dr. Garland implies that one should not make a diagnosis of disseminated sclerosis in two or more members of one family. In a controlled study[1] we have found 6.5% familial incidence and we know of no controlled study which refutes this finding. We cannot, however, claim that the familial factor is important in the aetiology. A similar familial incidence is found in diabetes mellitus; yet no one would consider changing the diagnosis of diabetes mellitus on account of a positive familial history.

Dr. Garland mentions Professor Platt's valuable suggestion that artificial feeding in infancy may play a part in the aetiology of disseminated sclerosis. We inquired into breast-feeding in our survey, and where a definite answer could be obtained we found that 90% of our patients had been breast-fed. However, we did not inquire how long this had been carried on. However, recently we came across a young woman in her twenties with undoubted disseminated sclerosis, who gave the startling information that she had been nursed at the breast for three years.—We are, etc.,

R. S. ALLISON.
J. H. D. MILLAR.

Belfast.

REFERENCE

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Food-poisoning

SIR,—I think that doctors in the public health service will have been struck by an air of unreality in Dr. Christopher Hardwick's article on "Acute Food-poisoning" (*Journal*, May 14, p. 1205). To say that "single cases and outbreaks of food-poisoning still occur with some frequency" seems a marked understatement to the M.O.H. who is recording them week by week without much intermission. Dr. Hardwick also says that outbreaks of bacillary dysentery due to *S. sonnei* "occur occasionally" and that various institutions provide the bulk of the cases. In actual fact, this is a constant disease, occurring week by week in the general population of a large town, much as scarlet fever and whooping-cough occur, all the year round.

We in the public health service are constantly saddened and baffled by the complete detachment of our clinical brethren from the wider aspects of medicine, and here is yet another example of the way in which clinical teachers seem to be quite unaware that facts and figures about the *present* situation await them at the end of a telephone in the local town hall.—I am, etc.,

CYRIL G. EASTWOOD.

Cambridge.

The Changing Face of Medicine

SIR,—I read with interest Professor Kennedy's presidential address as delivered to the Edinburgh Obstetrical Society and reported in the *Journal*, April 30, p. 1045. It contains a reference to the problem of National Service and the doctor, which I am sure was not made in a bad spirit but which would seem to indicate that the two years thus spent is a complete and utter waste of time in the majority of cases. I feel that this is an opinion widely held and upon which a little illumination is well overdue.

What has the R.A.M.C. to offer to the National Service medical officer? It cannot be denied that it provides for the regular and short-service officer facilities for post-graduate specialist study which are unrivalled in the civilian medical world. Obviously these facilities cannot be made available to the man who is there for two years only, and he has to be used exclusively to fulfil the military commitments of the country. But every effort is made to give the National Serviceman the sort of work he would like, if this is at all possible and provided he has sufficient experience to be able to carry it out.

He may go to a military hospital to serve in whichever specialty he may have had experience in. Here he will find abundant clinical material with every opportunity to learn and every encouragement to do so. Should he take advantage of this and mark his work with the attainment of a higher degree or part of it, he will find genuine pleasure at his success. There is no lack of helpful teaching and advice. Such special facilities which do exist he may make free use of. He may be posted as a general duty medical officer. Here he is virtually a general practitioner. Considering the age group of his patients it is not surprising that chronic ill-health is uncommon and many conditions practically non-existent—but he should find plenty to occupy his attention. For the rest, many will find themselves in close proximity to a civilian hospital. There is no Army regulation to stop them visiting such a place. It must be remembered that there is no compulsion on the National Service medical officer to improve his knowledge and ability beyond that necessary in the performance of his duties—much depends upon himself as it does in civilian practice. As a National Service officer myself I can say in all sincerity that I have received nothing other than help and encouragement during my period of service.

In conclusion I would like to make it clear that I do not suggest that a period of National Service is a benefit from the purely professional point of view, or that it is intended that it should be. It is a matter of personal initiative. If a man has no desire to learn and is content to vegetate then he has every right to do so and no one will compel him. In such circumstances, however, he is in no position to grumble and say that he has learned nothing and forgotten much. If a refresher course is needed on the completion of his service then it is completely and utterly his own unaided fault, and any vacuum which may exist is confined solely to that space between his ears.—I am, etc.,

G. T. TATE.

London, S.W.1.

The Ban on Heroin

SIR,—As some of the small fry of Dr. R. Hale-White's letter (*Journal*, May 21, p. 1277) we, too, wonder what is "the perfectly good substitute for heroin." It certainly is not morphine, amidone, pethidine, or codeine. We wonder whether the chairman of the Central Health Services Council and Lord Haden-Guest have heard of the Brompton mixture of heroin and cocaine for the relief of suffering of, for example, cancer of the lung, and, if they have, we wonder what they would substitute for it.—We are, etc.,

E. H. V. HENSLEY. G. SWIFT.
F. C. HEATLEY. J. A. PATERSON.
H. J. BLISS. G. FISHER.

Winchester.

SIR,—I am very concerned about the proposed Government ban on heroin (diamorphine) and would like to add my voice of protest to that of Dr. A. H. Douthwaite (*Journal*, April 9, p. 907). Here is our most potent weapon for the relief of pain to be denied us. Not only is heroin the most potent but often it is an irreplaceable drug. And heroin has other uses besides analgesic.

May I recall the case of a patient of mine—the victim of Buerger's disease? In the course of eight years this man had over forty operations, mostly amputations of major or minor extent and a sympathectomy, and now he has lost both legs and parts of all his fingers. During those eight years he suffered continuous pain of greater or less severity. When at its worst nothing could control it but heroin. Everything was tried—pethidine and the modern synthetic analgesics were useless, morphine was ineffective and made him sick. And he needed heroin in heroic doses. When the pain was at its worst he was taking heroin ¼ gr. (22 mg.) by injection every two hours, day and night for days on end—he and his wife gave the injections—4 gr. (0.26 g.) of heroin a day. At that he did not appear drugged, but felt and acted like a normal man; and it abolished his pain. One will say that he had become addicted to it. That is not so. If his pain eased up he would drop it in a day or two and do with something milder. Two years ago his disease became arrested, since when he has had no pain and no drugs. And the Government propose to deny us the use of this unique drug.

Fortunately my patient's disease is now quiescent, but it may flare up again.

Fortunately Buerger's disease is a rare condition, but there are others who suffer it. And there are other painful

conditions besides this. Our most powerful ally for the relief of pain is to be outlawed, but why is this being done? Because heroin addiction is a problem in America. I contend that this is not a justifiable reason for banning its use in this country. For one thing, it will not stop drug addiction in America. Further, there are other and better ways of controlling their addicts without interfering with us. Britain manufactures and exports heroin; there is no problem of addiction in this country. Surely American interests could be served by banning the export of the drug, though continuing its manufacture for home consumption.

Furthermore, note that all this has been done behind our backs. There was an annotation in the *Journal* of July 25, 1953 (p. 196), to the effect that W.H.O. had recommended that production and importation of diamorphine be abolished throughout the world. Since then nothing. Surely a step of such importance deserves some announcement in anticipation, perhaps a leading article in our official journal. The first printed word concerning it was a letter of protest by Dr. Douthwaite, after the Government decision had been made.

Also our legislators are being deceived. The subject has been brought up in the House of Lords (reported in the *Journal* of May 7, p. 1163), where Lord Mancroft said that "adequate supplies of a perfectly good substitute were now available." He has been deceived. There is no substitute for heroin. And, again, Lord Haden-Guest asserted that "the whole medical profession, so far as could be ascertained, was behind the order." That is untrue. Not only were the profession never consulted or asked their opinion, they were never even informed that such a step was being contemplated.

A week or two ago I placed these points before a meeting of the local Division of the British Medical Association—mainly to find out whether other doctors thought in this matter as I did. I was greatly gratified by the support my ideas received from them, and it was largely at the instigation of this meeting that I was encouraged to place my views before you.—I am, etc.,

Moffat, Dumfriesshire. W. J. GILLIES.

SIR,—Maybe those who favour the ban on heroin are also heroic in disapproving of any attempt to relieve nocturnal cough by prescribing a linctus. Some of us, however, will wonder what to give our coughing diabetics at night if our old friend and stand-by linct. diamorph. et hyoscyam. is to disappear. Probably one or other of the big drug firms will come to our rescue, but, as they seem to have run out of names which are easy to remember, we may find ourselves, particularly the older among us, groping vainly when we try to recall the title of their products.—I am, etc.,

Launceston. DONALD M. O'CONNOR.

Clinical Staging of Cancer of the Breast

SIR,—I would be grateful if you would allow me to comment upon the response to my letter on this subject which you, Sir, and the Editor of the *Lancet* were good enough to publish recently (*Journal*, March 26, p. 790). A copy of the letter and a covering note were sent to a surgeon and a radiotherapist at each of the teaching hospitals in Great Britain and to a number of interested clinicians. In all, sixty-five people were written to, and I asked not only for their personal views but suggested that they might feel inclined to bring the matter forward for discussion at their hospital medical committees. Forty-three replied, with varying degrees of enthusiasm, that they favoured the plan to establish an international staging and wished me luck, though several said it would be an uphill struggle. Two said it was hopeless trying and one said the attempt should not be made at all. The opinions most frequently expressed were that the British Empire Cancer Campaign, the Royal College of Surgeons, and the Faculty of Radiologists were the most appropriate bodies to deal with the matter. Mr. R. M. Blaikley has informed your readers (*Journal*, April 16, p. 970), and this has also been pointed out to me by individual correspondents as well as by the reports from medical committees which are beginning to reach me, that a committee of the General Register Office under the chairmanship of Dr. A. H. T. Robb-Smith is considering this subject at the moment. It seems, therefore, that the problem is actively exercising learned opinion, and it is certainly not the wish of my colleagues at the Royal Marsden Hospital, on whose behalf I first wrote, to complicate the issue further at present.

I think it is generally agreed that any staging must be clinical, although, as Dr. H. J. G. Bloom and Dr. W. W. Richardson point out (*Journal*, May 21, p. 1276), a pathological staging of the regional lymph nodes is much more accurate. But it is a fact that this information is not available in a high proportion of the cases, and their graph indicates that within each clinical stage what one loses in pathological grade 3 cases one gains in grade 1 cases. My personal view is that staging should only be clinical but that in the presentation of results the histology should also be considered when this is known. Dr. Robert Morrison's staging (*Journal*, May 7, p. 1153), employing as it does eleven groups, looks complex but is in fact an application of the T.N.M. system, which will undoubtedly form the basis of any international staging, not only for cancer of the breast but for other sites as well. I feel confident myself that an acceptable staging will emerge in the not-too-distant future.—I am, etc.,

London, W.1. MICHAEL HARMER.

Treatment of Severe Asthma

SIR,—In the article "Treatment of Severe Asthma" in the "Emergencies in General Practice" series (*Journal*, May 21, p. 1269) considerable space and attention have been given to A.C.T.H. and cortisone, remedies which are not likely to be available to the general practitioner called to treat an attack. Intravenous infusion is also often impracticable, as is the administration of oxygen.

In a short article for general practitioners I find it depressing that nearly a third of the space is devoted to the above-mentioned remedies whilst several useful and easily available drugs are omitted. Every doctor has his own particular drill for treating an acute asthmatic attack, but surely pethidine and paraldehyde warrant at least half as much space as cortisone and A.C.T.H.—I am, etc.,

London, S.E.2. PETER H. SHERWOOD.

Insecticide Vaporizers

SIR,—Your annotation on "Insecticide Vaporizers" (*Journal*, May 14, p. 1202) has over-simplified the case and fails to distinguish black from white. The impression is given that insecticide vaporizers originated in America and are only now coming into use in this country. The contrary is the case, for the first test of such equipment was made in the course of Admiralty trials of new insecticides in 1946, and as part of the programme the mammalian toxicity of a "continuous-flow aerosol" was investigated.[1]

Arrangements were soon made for manufacture in the U.S.A., and in both countries this original apparatus has been in use on an ever-increasing scale with great success and no single recorded case of harm to a human being.

Your annotation is, of necessity, based on American sources, and it is a regrettable fact that the situation in the U.S.A., following the introduction of the original British-designed apparatus, rapidly got out of hand, and it is believed that there are now over 90 different and indifferent copies of the original. At this point the vital importance of discriminating between correctly designed equipment and copies based on insufficient technical and scientific knowledge must be very strongly stressed. The A.M.A. Committee on Pesticides noted that few machines conformed to what was considered to be a reasonably safe design, and herein lies the reason for such cases of illness attributed to the "vapours" that have so far been reported in the U.S.A. The reverse is the case in Britain, for by far the greatest number of vaporizers in use in this country are the

product of very careful design and strict control over the output and insecticides used. All these units conform to, and in performance are well within, the limits stated by the A.M.A. Committee for insecticide vaporizers and the Canadian Standards Association.

Your statement on the fluctuating performance of a unit subjected to local air currents is misleading, for the essential point has been entirely missed, as the outputs referred to a unit in which the thermostat was known (and stated) to be wrongly placed. This was, in fact, part of the experimental work carried out at the University of Massachusetts on behalf of the original American company.[2]

Barnes[3] and Brown[4] testify to the safety of both D.D.T. and B.H.C. in general use, and Princi[5] sums up recent work on D.D.T.: "Most scientists to-day agree that the danger of chronic toxicity from D.D.T. exposure is negligible," and more recently still in a leading article on "Agricultural Poisons" (*Journal*, April 2, p. 836) you commented as follows: "Although D.D.T., chlordane, B.H.C., and similar substances have been used in considerable quantities in many parts of the world, there is no evidence to suggest that persons using them as insecticides suffer any serious risk of acute or chronic poisoning." The experiment cited in which rats were affected when exposed to continuous inhalation falls into its proper perspective when it is realized that the dosage was appreciably greater than that possible with the majority of British vaporizers correctly sited and installed, and the fact that they have been used for much longer periods in a number of laboratory animal houses for the control of flies and body parasites with great success and perfect safety, and that one important installation has been in continuous use for nearly two and a half years.

Finally, I must refute your statement as to the ineffectiveness of such vaporizers. It is impossible in the space permitted to do more than state that the continuous-flow aerosol is a highly effective method of pest control in enclosed spaces and to give a few references, in particular the generalized account of the method in its application in many fields which has been published in *The Times Review of Industry*.[6–13]—I am, etc.,

F. G. SAREL WHITFIELD.

Avebury Research Laboratories,
Avebury, Oxon.

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11 Baker, A. H., ibid., December, 1952, p. 24.
12 Whitfield, F. G. S., *et al.*, ibid., April, 1953, pp. 24 and 32.
13 —— —— ibid., April, 1954, pp. 24 and 29.

Labelling the Container

SIR,—I wonder whether the time has not come to do away with the custom—peculiar to this country, I believe—to label medicine containers so that neither patient nor doctor can assess their contents. May I suggest that, on the contrary, it should be made compulsory for the chemist to label every medicine in such a way that its composition is clearly and fully described on the container?

As far as I can see it serves no useful purpose to keep the patient in ignorance of the nature of the medicine he is taking. The time should have passed when ignorance may have been thought to have therapeutic value, and to be a welcome help to ensure the superiority of the doctor. If the doctor's prescription does not satisfy the possibly critical mind of the patient nothing is lost by explaining the matter, or even by thinking twice before prescribing. Conversely, I cannot see any possible harm arising from the fact that the patient knows the ingredients of the medicine he is taking. There is no place in present-day medicine for the use of coloured water or other miracle drugs; besides, in the case of placebos or for special reasons, the chemist could always be advised how to label the medicine. It happens not seldom that medicines are mixed up in the household and that the wrong drug is taken or given to children. This would occur less frequently. Even errors in dispensing may more easily be discovered if the container is labelled by the chemist.

Much of the doctor's time and mental energy would be saved if he were not so often confronted with bottles of tablets or medicine and expected to decide on sight which of them should be continued and which should be stopped; or if he were not asked to repeat the prescription for the "medium-sized" white tablets of which the patient has run out; or if he were spared the efforts he has to make when he wants to know which drugs other doctors or the hospital had previously prescribed. The patient would less often be treated with drugs which had already proved to be useless, and the State and the private patient would save appreciable sums of money if the identity of the medicine in the private medicine cupboard, in which highly expensive drugs such as antibiotics and hormone preparations often live a long and useless life, could be assessed, and if these drugs could be used when they are again needed.—I am, etc.,

London, W.1. H. UCKO.

Cases Wanted

SIR,—In October, 1954, Kurtzke and Berlin[1] reported favourably on the use of isoniazid in a small series of cases (30) of multiple sclerosis. The results were sufficiently encouraging to warrant a therapeutic trial, and this is now being carried out in four hospitals—Middlesex Hospital, London, W.1; the Maida Vale Hospital for Nervous Diseases, London, W.9; Bristol Royal Infirmary (Dr. A. M. G. Campbell); and the Royal Victoria Hospital, Belfast (Dr. R. S. Allison).

The trial is limited to cases of recent onset, including retrobulbar neuritis, and those with a recent relapse who were capable of walking half a mile before the relapse. Cases are admitted for a period varying from two to four weeks. The trial is blind—that is, the clinician in charge of the case does not know if the patient is receiving isoniazid or the control drug, arsenic, since both substances are used in identical tablet form.

In order to expedite the entry of cases into this trial it is hoped that general practitioners will refer suitable cases to one of the above hospitals.—I am, etc.,

London, W.1. DOUGLAS MCALPINE.

REFERENCE

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Technique of Psycho-analysis

SIR,—In view of the extremely friendly and laudatory nature of Dr. Ernest Jones's review of my *Technique of Psycho-analysis* (*Journal*, May 21, p. 1261) it may seem a little ungracious to correct him on a minor point of fact. Dr. Jones maintains that, since the first edition of this book was published in 1928, "Dr. Glover has severed his connexion with other psycho-analysts." This is not quite accurate enough. In 1944, owing to my conviction that the orientations of an increasing section of the British Psycho-analytical Society, and consequently of its training system, had become profoundly unscientific, I demitted my offices in, and membership of, that Society. To mark the continuance of my relations with other psycho-analysts and with the International Association, I sought for and obtained membership of the Swiss Psycho-analytical Society. About the same time I was made an honorary member of the American Psycho-analytical Association, and subsequently was appointed chairman of the then Research Committee of the International Association. A small point, perhaps, but of some scientific and professional moment to me.—I am, etc.,

London, W.1. EDWARD GLOVER.

Obituary

E. A. RENNER, O.B.E., M.B., Ch.B.

Dr. E. A. Renner, director of medical services of Sierra Leone, died in London on April 28 at the age of 60.

Edowo Awunor Renner was born at Freetown, Sierra Leone, on June 3, 1894, the son of Dr. W. A. Renner, who had served for 33 years in the medical service of the Colony and who had acted as principal medical officer, as the director was then termed. E. A. Renner's early education was received at the Boys' High School, Freetown, and was interspersed with regular visits to his grandparents, who had retired to Jersey, in the Channel Islands. Later he was a pupil at Park Field School, Sefton Park, Liverpool, and he went on to become a medical student at Edinburgh University, where he graduated M.B., Ch.B. in 1919.

Renner was always interested in the welfare of his own people, and he joined the Sierra Leone medical service in 1920. During his 35 years of devoted service he was medical officer in many of the medical stations throughout the Colony and Protectorate, and at one period of his career he was in charge of the pathological laboratory. During the latter part of his clinical career he was stationed at Freetown as senior medical officer in charge of the Maternity Hospital, and was also a much sought after and highly respected private practitioner in that city. For his public-spirited work he was appointed O.B.E. in 1948. Apart from his clinical acumen, he displayed outstanding administrative ability, which, combined with great tact and a very pleasant manner, endeared him to everyone. He was promoted deputy director in 1950, and a year later director of medical services of Sierra Leone, and was therefore the first African director of medical services in any of the West African colonies.

Renner was appointed director at a very difficult time, when the post-war shortage of staff and constitutional changes in the Colony added to the responsibilities of the director. His tact and preparedness to appreciate the views of the other man without sacrificing his own principles were no doubt of great value to the Colony and to the medical department, and without him much could not have been accomplished. Despite his onerous duties he found time to interest himself in the Red Cross, to which he rendered valuable service, and he was also a very keen freemason and churchman. "Teddy" Renner, as he was affectionately called by all his friends, will be greatly missed, and it is a tragedy that he died before he could enjoy a well-earned retirement with his family in England. He leaves a widow and four children, his eldest son being in medical practice in Beaconsfield.—F. McL.

A. J. WILSON, M.D., F.R.C.P.Ed.

The obituary of Dr. A. J. Wilson was printed in the *Journal* of May 21 (p. 1285). We are indebted to Dr. J. SHULMAN for the following appreciation :

By any assessment Arthur J. Wilson was remarkable. By rigid assessment he was a man of unusual talents and character. During the first world war his medical studies were interrupted by service in the Royal Flying Corps, in which he was for a time an instructor in aerial gunnery. I first met him in 1922, when we were fellow residents at the Coventry and Warwickshire Hospital. I am proud to think that our friendship, established then, endured to the time of his death. From the very onset of his professional career he was outstanding. His life was a model of spartan simplicity—even as a young hospital resident it was obvious that he had a definite objective in life which nothing could deter him from achieving. Self-discipline was so firmly established in his character in these early days that he rapidly earned an enviable reputation for early rising, punctuality, precision, and accuracy—neatness and tidiness dominated every activity. His very handwriting was so neat and legible that throughout his life it was always a pleasure for others to read his medical notes. Clinical work followed the same pattern, and so careful and accurate were his observations that in all the 33 years of our acquaintance I have not known a diagnosis, once established by him, ever amended by anyone else. Ill-health unfortunately dogged his early professional career, and, advised by Sir Robert Philip, he showed rare courage in deciding to practise as a physician consultant at a time when it was almost a dangerous experiment so to do. He was by this time honorary physician to the Coventry and Warwickshire Hospital and was a pioneer in establishing the department of cardiology there. It was only natural, with his sound knowledge, accompanied by the most scrupulously careful and patient clinical observations, that he rapidly built up an undisputed reputation for reliability among practitioners and colleagues. Simple spartan tastes never deserted him. Apart from music and photography, medicine was his only hobby. Self-discipline was so firmly engendered that no one ever knew him to utter an angry or unkind word. This gentleness, accompanied by a charming simplicity of manner, always made him a most delightful listener, and he extended this quality to all his patients. For those who knew him his memory will be green for many a day.

Dr. W. J. GRANT, who was in practice at Shrewsbury for nearly 33 years, died at his home there on March 28 at the age of 63. William James Grant was born in Prince Edward Island, Canada, on January 31, 1892, and was educated at St. Dunstan's College, Charlottetown, Prince Edward Island, and at Laval University, Quebec, where, in 1909, he obtained the certificate of B.A. which entitled him to begin his professional studies in medicine. He entered McGill University, Montreal, for this purpose, and graduated M.D., C.M. in 1914, after which he held a resident appointment at the Western General Hospital, Montreal. From 1915 to 1919 he served first in the R.A.M.C. and then in the R.C.A.M.C., and on return to civilian life he decided to make his home in England, and for a short time was honorary assistant surgeon at Croydon General Hospital. He obtained the F.R.C.S.Ed. in 1921, and in the following year entered into partnership with Dr. J. D. Williams at Shrewsbury. When Dr. Williams retired soon afterwards Dr. Grant took over the whole of the practice. Dr. Grant was exceptionally knowledgeable and well read in medico-political matters. While his views were not always shared by his colleagues in Shropshire, his presence at local meetings never failed to add interest and fire to the proceedings. For some time he was a member of the executive committee of the Fellowship for Freedom in Medicine, and, although he had to resign from the committee because of the distance he had to travel to attend meetings, he remained a staunch supporter of the Fellowship. He will be remembered for his determined fight to secure better remuneration under the Danckwerts award for the single-handed practitioner with a small list of patients, a fight which was crowned with success. He was one of the signatories to the requisition which, in 1953, called for an extraordinary general meeting of the British Medical Association, and it was he who submitted the main pleading on behalf of the small-list practitioner at that meeting. Dr. Grant was chairman of the local committee of the British Medical Guild; he was also a member of the Shrewsbury medical board and for the past few years its chairman, and a member of the Industrial Injuries

Disablement Board of the Ministry of Pensions and National Insurance. With the full knowledge of the hopelessness of his final illness, he bore it with great fortitude. He is survived by his widow, two sons, and two daughters.—A. G. W.

Medico-Legal

"AUTOMATISM" AS A DEFENCE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On February 11, 1955, Stanley Charlson was tried before Mr. Justice Barry and a jury at Chester Assizes on charges of causing grievous bodily harm with intent to murder or with intent to cause grievous bodily harm, and of unlawfully wounding his 10-year-old son Peter.[1]

Charlson's family medical background was that his mother had died of a cerebral haemorrhage, his aunt of a cerebral tumour, and his sister of meningitis. He himself some six years before had had trouble with his legs, which he had been told was neuritis, and since then had had increasing weakness in his legs and difficulty in co-ordinating their movements if he tried to walk fast or run. He also had had persistent headaches, sometimes of great severity. On examination by the prison doctor he was found to have signs of organic disorder of the nervous system pointing to the possibility of a cerebral tumour, though the doctor did not make a definite diagnosis. There was no question of any "disease of the mind."

Charlson, who was a devoted husband and father and on excellent terms with his son, had called Peter into the back room of their home to see a rat which was standing on a stone in the river. He then for no apparent reason picked up a wooden mallet from the floor, struck him twice on the head, breaking the skin of the scalp and causing blood to flow, and then threw him out of the window 25 ft. (8 m.) into the river, severely injuring his arm and leg. When interviewed by the police later in the day, Charlson was dazed and bewildered and knew that he had done something dreadful. He remembered hitting Peter with the mallet in the back room, but could not think why he had done so.

Mr. Justice Barry in summing up to the jury told them that no defence of insanity was raised in the case. It was, however, for the prosecution to prove on the first two charges that Charlson had had the intent specified in the charge—namely, to murder Peter or cause him grievous bodily harm. On the third charge, of unlawful wounding, the prosecution would have to prove no more than that when he struck the blows he knew what he was doing. However, if he did not know what he was doing, if his actions were purely automatic and his mind had had no control over the movement of his limbs, if he was in the same position as a person in an epileptic fit, then no legal responsibility for his act rested upon him at all. The prison doctor had given evidence that someone suffering from a cerebral tumour is liable to outbursts of impulsive violence over which he would have no control and which would be quite without motive, and that Charlson's conduct was wholly consistent with such a condition.

The jury returned a verdict of "Not Guilty" on all three charges.

FEMUR FRACTURED DURING E.C.T.

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On March 31, 1955, Mr. Israel Weingott, a tailor, withdrew an action against Dr. Dalton E. Sands and the Board of Governors of King's College Hospital on the second day of the hearing. Mr. Weingott's case had been that electric convulsion therapy had been administered to him under Dr. Sands's supervision while sitting in a chair instead of lying down, resulting in a fracture of his left femur.

Mr. Weingott gave evidence that he was sitting in a chair before the treatment, in the course of which he became unconscious. Dr. Rossiter Lewis, called as expert witness on his behalf, said that the essential principles to be observed during E.C.T. were that the patient should be flat on his back on a bed or couch of firm consistency and in a position to be properly controlled by assistants at his head and feet or in some kind of restraining jacket to prevent violent movements of the legs. It was possible for the patient to suffer a broken femur during treatment even if these principles were observed. The risk would be greatly increased if the treatment were given to the patient sitting in a chair.

A former porter at the hospital gave evidence that on the day on which the treatment was given he took Mr. Weingott straight to the cubicle in which he was to have his treatment, and that this contained a wooden armchair but no couch. He said that later he collected him from the cubicle on a trolley and took him to the casualty department for his fractured femur to be treated. In cross-examination he was unable to explain how he came to do this when his time sheets showed that he was not on duty on the day in question.

Announcing the withdrawal of the case Mr. Weingott's counsel said that Mr. Weingott having heard the evidence was satisfied that there was no foundation for any of the charges of negligence he had made against the doctor and the hospital. The Lord Chief Justice said that the most serious thing was the allegation against the doctor, and he had been very glad to hear it withdrawn. Although he felt that the plaintiff had been entirely honest in bringing the action, he had obviously suffered from mental trouble, and his evidence was not such that he would have acted on it. There would be judgment for the defendants with costs.

The Medical Defence Union instructed Messrs. Hempsons, solicitors, to act for Dr. Sands.

[1] 1955 1 *Weekly Law Reports*, p. 317.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. R. M. Acheson has been elected to a Radcliffe Travelling Fellowship, and Dr. R. G. Tucker has been awarded the Radcliffe Prize.

Mr. H. J. R. Beveridge (Ampleforth College) has been elected to a Nuffield Scholarship in Medicine at Pembroke College.

In Congregation on April 28 the degree of D.M. was conferred on Mrs. Zaida M. Hall and, in absence, on Constance L. Simpson.

Dr. J. L. Gowans has been elected to the Staines Medical Research Fellowship at Exeter College as from October 1, 1955.

UNIVERSITY OF CAMBRIDGE

The following degrees were conferred in Congregation on April 30:

M.D.—E. H. R. Ford.
M.B.—J. R. Burwell.

In Congregation on May 14 the following degrees were conferred:

M.A.—R. A. Parker, M.B., B.S.
M.B., B.CHIR.—L. M. Barrett.
M.B.—J. S. Garfield (by proxy).

Drs. John Hugh Ross and Richard Hume Adrian have been elected to Fellowships at Corpus Christi College.

UNIVERSITY OF GLASGOW

The following degrees were conferred on April 30:

M.D.—M. C. Macleod (with honours), R. C. MacLeod.
PH.D.—T. C. D. Whiteside, M.B., CH.B.

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

The following degrees were conferred on May 12:

M.D.—Margaret K. B. Knox, E. du P. Meiring.
M.B., B.CH., B.A.O.—P. R. D. Black, Jean R. Ellis, A. C. A. Hempel.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 14** (No. 19) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	9	0	7	0		9	0	4	1	2
Dysentery	1,038	53	409	13		1,031	153	335	6	1
Encephalitis, acute	4	0		0		5	0	0	0	
Enteric fever: Typhoid	2	1	2	0		3	1	0	0	0
Paratyphoid	12	0	3	0		7	0	1	0	0
Food-poisoning	211	40		3		240	22		0	
Infective enteritis or diarrhoea under 2 years				10	17				8	20
Measles*	20,384	1063	254	290	273	1,706	58	169	121	332
Meningococcal infection	22	1	15	1		35	5	15	0	1
Ophthalmia neonatorum	45	3	5	1		29	4	12	0	
Pneumonia†	441	25	170	2	5	463	35	196	5	2
Poliomyelitis, acute: Paralytic	11	2	1	1	1	14	0	2	1	
Non-paralytic	5	0				5	1			
Puerperal fever§	274	36	2	1		258	43	14	1	
Scarlet fever	571	27	66	42	13	898	54	110	32	43
Tuberculosis: Respiratory	823	107	186	35		816	91	170	21	
Non-respiratory	127	10	25	7		118	6	26	3	
Whooping-cough	1,805	75	137	49	28	2,660	85	308	47	39

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0	0		0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	1	0	0	9	0	1	1	0
Influenza	10	1	0	0	2	10	2	0	2	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	175	17	18	11	11	200	41	25	19	9
Poliomyelitis, acute	1	0			0	0	0	0		0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory	73	14	9	0	5	86	11	13	2	9
Non-respiratory		1	1	0	0			1	0	2
Whooping-cough	1	0	0	0	0	2	0	0	1	0
Deaths 0–1 year	197	36	23	10	15	249	28	30	8	17
Deaths (excluding stillbirths)	5,026	680	563	111	168	5,441	755	637	139	180
LIVE BIRTHS	7,669	1185	926	258	433	8,016	1216	962	235	445
STILLBIRTHS	186	23	23			207	21	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in April was 116, compared with 113 (revised figure) in the previous month and 107 (revised figure) in April, 1954.

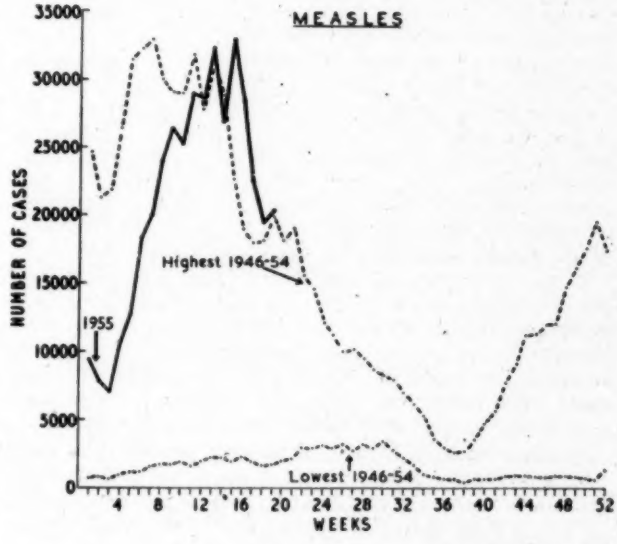
The numbers of cases of industrial diseases in the United Kingdom reported during April, 1955, were as follows: lead poisoning 5, anthrax 1, epitheliomatous ulceration 15, chrome ulceration 26; total 47. There were no deaths.—*Ministry of Labour Gazette*, May, 1955.

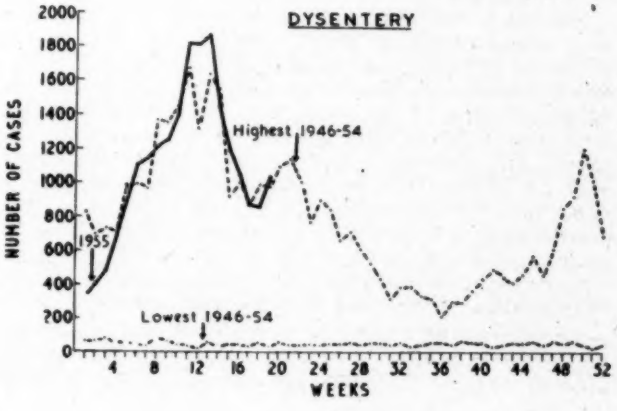
Week Ending May 21

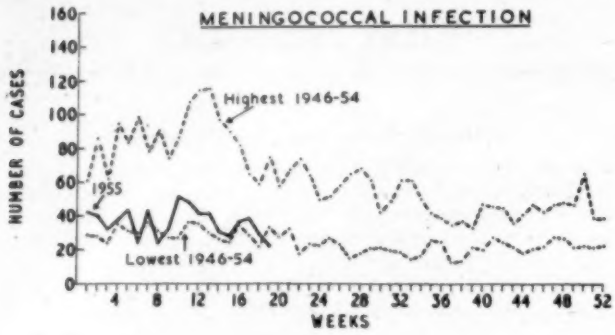
The notifications of infectious diseases during the week included: scarlet fever 620, whooping-cough 1,613, diphtheria 17, measles 23,655, acute pneumonia 377, acute poliomyelitis 19, dysentery 1,232, paratyphoid fever 7, and typhoid fever 3.

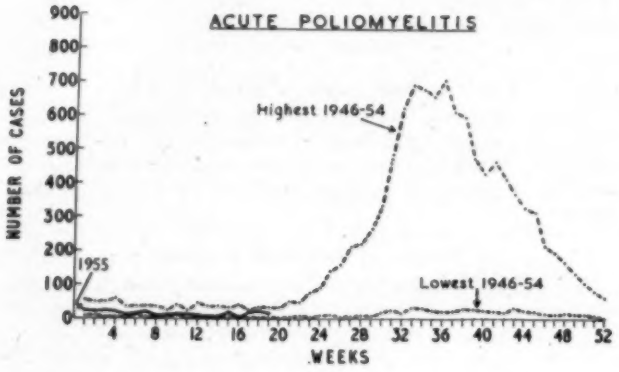
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest rises in the number of notifications of infectious diseases in England and Wales during the week ending May 14 were 892 for measles, from 19,492 to 20,384, and 176 for dysentery, from 862 to 1,038, and the largest falls were 58 for acute pneumonia, from 499 to 441, and 45 for whooping-cough, from 1,850 to 1,805.

The largest increases in the incidence of measles were 427 in Leicestershire, from 472 to 899, 303 in Glamorganshire, from 693 to 996, 256 in Kent, from 600 to 856, and 213 in Southampton County, from 735 to 948, and the largest decreases were 292 in Middlesex, from 1,606 to 1,314, 276 in Yorkshire West Riding, from 2,143 to 1,867, 232 in Warwickshire, from 1,631 to 1,399, and 216 in Essex, from 1,269 to 1,053. 571 cases of scarlet fever, 4 fewer than in the preceding week, were notified, and there were no large fluctuations in the local trends. Only small changes were reported in the returns for whooping-cough. 9 cases of diphtheria were notified, being 5 more than in the preceding week. The areas with more than one case of diphtheria were Kingston-upon-Hull C.B. 3 and Liverpool C.B. 2.

16 cases of acute poliomyelitis were notified, and these were 3 fewer for paralytic and 5 fewer for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 3, London 2, Wiltshire 2, Warwickshire 2 (Birmingham C.B. 2).

The rise in the notifications of dysentery was mainly due to a large outbreak in Surrey, Croydon C.B. The largest centres of infection were Lancashire 339 (Liverpool C.B. 53, Blackburn C.B. 49, Manchester C.B. 45, Oldham C.B. 39, Middleton M.B. 19, Blackpool C.B. 18, Whiston R.D. 16, Crompton U.D. 13, Salford C.B. 11, Rochdale C.B. 10), Surrey 162 (Croydon C.B. 147), Durham 107 (Easington R.D. 23, Stanley U.D. 19, Seaham U.D. 17, South Shields C.B. 10), Northumberland 75 (Castle Ward R.D. 36, Newcastle-upon-Tyne C.B. 22), Yorkshire West Riding 62 (Huddersfield C.B. 29, Leeds C.B. 11), London 53 (Islington 16), Yorkshire North Riding 42 (Middlesbrough C.B. 38), Warwickshire 24 (Coventry C.B. 14), and Middlesex 22.

In Scotland the number of notifications of dysentery increased by 16 to 409. The largest returns were those of the cities of Glasgow 224, Edinburgh 46, and Dundee 37.

Medical News

Westminster Hospital Old Students' Dinner.—The annual Westminster Hospital dinner was held on May 27 at the Royal College of Surgeons. A large gathering, said to be a record, assembled to support the chairman, Dr. F. M. ALLCHIN. In proposing the toast of Westminster Hospital and Westminster Medical School, the chairman said that the school was full and that there were 500 applications a year for the 60 vacancies. Mr. F. A. D'ABREU proposed the toast of the guests, for whom Sir DANIEL DAVIES replied. Sir STANFORD CADE proposed the health of the chairman, and his speech, like Dr. Allchin's in reply, was a mixture of sentiment and reminiscence suitable to such an occasion.

Prison M.O.s.—The Annual Conference of Prison Medical Officers and Psychologists was held at the Home Office on May 20, the chair being taken by Dr. H. K. SNELL, Director of Medical Services, Prison Commission. Dr. J. D. W. PEARCE, of St. Mary's Hospital, and Mr. EDWARD CLARKE, barrister-at-law, spoke on "The Value of Statements Elicited During Conditions of Altered Consciousness Artificially Induced." Dr. I. A. ANGUS, Dr. W. A. NORTON, and Mrs. A. SMITH, of the Brixton Prison staff, contributed a paper on "Observations on Eleven Cases of G.P.I. at Brixton," and Dr. C. F. T. SAVILLE, medical officer at Aylesbury Borstal Institution, read a paper on "A Visit to Some Spanish Prisons."

The Society of Physicians in Wales held its sixth meeting at Tenby on May 13–14 under the chairmanship of Dr. JOHN DE SWIET. The following papers were read: "Leptospirosis in Pembrokeshire," by Dr. GLAN DAVIES. "Carpal Tunnel Syndrome," by Dr. GEOFFREY LLOYD. "Treatment of Severe Hypertension by Oral Medication," by Dr. JOHN FORBES. "Some Observations on Thrombocytopenia," by Professor SCARBOROUGH. "Experimental Embolic Carditis," by Dr. ANEURIN HUGHES. "Perforation of Interventricular Septum in Myocardial Infarction," by Dr. J. M. SWITHINBANK. "Electrocardiographic Changes in Pulmonary Embolism," by Dr. J. DE SWIET.

Royal Society Awards.—Under the Royal Society and Nuffield Foundation Commonwealth Bursaries Scheme, Mr. D. H. COLLESS (University of Malaya) receives an award to enable him to study the systematics of mosquitoes at the Natural History Museum; Dr. A. A. KINNEAR (University of Pretoria) to enable him to study endocrinological techniques at Birmingham; and Dr. J. H. D. MILLAR (consultant neurologist, Belfast) to enable him to study electrocorticography at the Montreal Neurological Institute.

R.S.I. Elections.—The following medical men have been elected to the council of the Royal Sanitary Institute: Dr. E. HUGHES, Dr. A. G. G. THOMPSON.

Dr. J. H. F. Brotherston has been appointed professor of public health and social medicine at the University of Edinburgh in succession to Professor F. A. E. Crew, F.R.S., who retires on September 20. Dr. Brotherston is aged 40, and qualified at Edinburgh in 1940. After service with the R.A.M.C. during the war, he worked at the London School of Hygiene and Tropical Medicine, and at Guy's Hospital.

Dr. C. V. Harrison, of the London Postgraduate Medical School, has been appointed professor of morbid anatomy in the University of London.

New French Neurosurgical Journal.—Messrs. Masson and Co. announce the publication of a new quarterly journal, *Neuro-Chirurgie*. The journal is sponsored by the Société de Neuro-Chirurgie de Langue Française, but will also publish papers by authors who are not members of this society. Subscription is £4 12s. 6d. per annum, and the journal is published from 120, Boulevard Saint-Germain, Paris, 6.

COMING EVENTS

Hammersmith Hospital and Postgraduate Medical School.—The golden jubilee of Hammersmith Hospital and the twentieth anniversary of the founding of the Postgraduate Medical School are being celebrated next week. The Queen is to visit the hospital and medical school on June 6, and June 8 will be an "open day", (from 2.30 to 5.30 p.m.), when special arrangements are being made to show interested doctors the work which is going on. Points of interest will include a new metabolic unit for the investigation of metabolic disorders, the Medical Research Council's cyclotron and linear accelerator, an exhibition illustrating the research work of the medical school, and a radio-isotope laboratory. Medical films will be shown in the lower lecture theatre, which will be the assembly point from which groups will be collected for conducted tours of the medical school and hospital.

A celebration ball will be held at the Park Lane Hotel on Thursday, June 9. Tickets (30s. including supper) can be obtained from Mr. J. G. BRICE, F.R.C.S., Hammersmith Hospital, London, W.12.

Royal Society of Tropical Medicine and Hygiene.—The Annual General Meeting will be held on June 15 (changed from June 16) at Manson House, 26, Portland Place, London, W.1, 7.30 p.m.

NEW ISSUES

Journal of Clinical Pathology.—The new issue (Vol. 8, No. 2) is now available. The contents include:

HISTOLOGICAL DIFFERENTIATION BETWEEN PHAEOCROMOCYTOMA AND MELANOMA OF THE SUPRARENAL GLAND. John C. Dick, Grace M. Ritchie, and Henry Thompson.

RETICULUM-CELLED MEDULLARY RETICULOSIS IN A YOUNG ADULT. F. G. J. Hayhoe.

NASOPHARYNGEAL PLASMACYTOMA WITH EXTENSIVE SKIN METASTASES. D. Emslie-Smith, J. M. Johnstone, and I. C. Whyte.

GLYCOGEN STORAGE IN THE LIVER IN DIABETES MELLITUS. R. Winston Evans, T. R. Littler, and H. S. Pemberton.

CYTOLOGICAL EXAMINATION OF SPUTUM IN RELATION TO ITS MACROSCOPIC PURULENCE. G. A. Rawlins.

THE DRIED DISC TECHNIQUE WITH BACITRACIN, CARBOMYCIN, ERYTHROMYCIN, POLYMYXIN B, AND TETRACYCLINE. R. W. Fairbrother and R. C. Jennings.

SENSITIVITY TESTS FOR THE POLYMYXINS. S. R. M. Bushby.

FURADANTIN IN PROTEUS BACILLURIA. S. J. Heffernan, P. W. Kippax, and W. A. V. Pamplin.

A CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF THE THREE BILE PIGMENTS IN SERUM. Barbara H. Billing.

THE THREE SERUM BILE PIGMENTS IN OBSTRUCTIVE JAUNDICE AND HEPATITIS. Barbara H. Billing.

AN INVESTIGATION OF SERUM LIPIDS AND LIPOPROTEINS BY PAPER ELECTROPHORESIS. W. G. Dangerfield and E. B. Smith.

THE RELIABILITY OF THE DETERMINATION OF URINARY PROTEINS BY ELECTROPHORESIS ON FILTER PAPER. D. Wolvius and J. C. M. Verschure.

AN APPARATUS FOR PAPER ELECTROPHORESIS. G. T. Franglen, N. H. Martin, and J. D. Treherne.

THE USE OF BORATE BUFFER IN PAPER ELECTROPHORESIS OF SERUM. R. Consden and Myfanwy N. Powell.

AMINO-ACID COMPOSITION OF SERUM PROTEINS IN HEALTH AND DISEASE. A. J. Cummings and F. V. Flynn.

PLASMA CREATININE. Mary Ralston.

AN ASSESSMENT OF NEW TESTS FOR DETECTING BILIRUBIN IN URINE. Daphne Bryant and F. V. Flynn.

UPTAKE OF SULPHATE ^{35}S BY LEUKAEMIC HUMAN BONE MARROW *in vivo*. F. Ellis, L. G. Lajtha, and R. Oliver.

HAEMORRHAGIC DIATHESIS DUE TO A CIRCULATING ANTICOAGULANT INVESTIGATED BY THE THROMBOPLASTIN GENERATION TEST. D. M. D. Evans.

THE EFFECT OF ANTIBIOTICS ON THROMBOPLASTIN GENERATION. W. N. Bell and H. G. Alton.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 6

●GUY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Carbutt Memorial Lecture by Dr. J. M. H. Campbell: Acyanotic Congenital Heart Disease.

INSTITUTE OF DERMATOLOGY.—June 6 to 30, semi-permanent exhibition: Some Interesting Photographs and Moulages (Department of Medical Illustration).

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—4.30 p.m., Mr. W. Hawksworth: Utero-vaginal Prolapse.

Tuesday, June 7

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: Vulval Atrophy.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Professor B. Ephrussi (Paris): Intrinsic Factors Controlling the Synthesis of Cytochromes in Yeast.

Wednesday, June 8

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Moniliasis and Related Diseases.

●LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE.—3 p.m., University Extension Lecture by Dr. J. A. Scott: Public Health in an Urban Community.

Thursday, June 9

BRITISH SOCIETY FOR RESEARCH IN AGEING.—At Ciba Foundation, 41, Portland Place, W., 2 p.m., symposium: Endocrinology and Ageing. Dr. V. Korenchevsky: Endocrinological Factors in Ageing; Dr. J. A. Loraine: Hormal Relations in the Menopause; Dr. P. L. Krohn: The Ageing Ovary; Dr. P. J. Thung, Dr. L. Boot, and Dr. O. Muhlbock (Amsterdam): Old Age Changes in the Morphology and Functions of the Mouse Ovary.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Benign Epithelial Tumours.

NORTH-WESTERN TUBERCULOSIS SOCIETY.—At Wrightington Hospital, Appley Bridge, Wigan, 3 p.m., summer meeting.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Mr. W. Gissane: Some Problems in the Treatment of Injuries.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Felope de la Balze (Buenos Aires): Some Histological and Functional Aspects of Normal and Pathological Testes.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor Milroy Paul (Colombo): Haemorrhages from Head Injuries.

ROYAL SOCIETY.—11 a.m., discussion to be opened by Professor H. S. W. Massey, F.R.S.: Radiative Balance in the Atmosphere.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Professor H. A. Salvesen (Oslo): Relation of the Parathyroids to Bone Metabolism and Bone Disease.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration in psychiatry.

Friday, June 10

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. G. B. Dowling.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. G. Scadding.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—3 p.m., Mr. A. H. C. Walker: Obstetric Fistulae.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Mr. P. McG. Moffatt: Use of the Ophthalmoscope in Medicine (I).

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., Professor O. Krayer (Harvard Medical School): New Aspects of the Pharmacology of Veratrum Alkaloids: The Anti-accelerator Cardiac Action of the Secondary Amines.

WHITTINGTON HOSPITAL.—At Archway Wing, N., 5.15 p.m., clinical pathological conference. Dr. J. M. Alstow: The Community, the Profession, and the Hospital.

APPOINTMENTS

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—B. H. Brock, M.B., B.Chir., F.R.C.S., Registrar in Orthopaedic and Traumatic Surgery at Winford Orthopaedic Hospital and United Bristol Hospitals; T. Galla, M.B., Ch.B., D.P.M., Senior Registrar in Psychiatry at the Bristol Mental Hospitals; S. Haroon, M.B., B.S., D.G.O., Registrar in Obstetrics and Gynaecology at Gloucestershire Royal Hospital, Gloucester; J. J. Y. Dawson, M.D., M.R.C.P., Senior Consultant Chest Physician to Plymouth Clinical Area; B. M. Hibbard, M.B., B.S., D.Obst.R.C.O.G., Registrar in Obstetrics and Gynaecology to Bath Group of Hospitals; W. Lumsden Walker, M.B., Ch.B., D.P.H., D.P.M., Medical Superintendent to the Hortham-Brentry Hospital Group, Bristol; T. C. Leahy, M.B., B.Ch., Senior Hospital Medical Officer to the Hortham-Brentry Hospital Group, Bristol; R. V. Walley, M.B., B.Chir., Deputy Resident Physician (Infectious Diseases), at Ham Green Hospital, near Bristol; J. R. Moyle, M.R.C.S., L.R.C.P., D.M.R.D., Consultant Radiologist to Plymouth Clinical Area; B. Chudecki, Med.Dipl., Cracow, Assistant Radiotherapist to Exeter Clinical Area.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Jacobs.—On May 11, 1955, at Arnold House, Arnold, Notts, to Jean (formerly Thwaites), wife of Dr. Brendan Jacobs, a son—Stephen Brendan.

Perren.—On May 4, 1955, at Battledown Manor, Cheltenham, Glos, to Mary, wife of Dr. John F. Perren, R.A.F., a son—Timothy John (corrected announcement).

Picken.—On May 23, 1955, at Cardiff, to Lisel (formerly Regensteiner), wife of David K. W. Picken, M.B., F.F.A. R.C.S., a brother for Charles—Ralph.

DEATHS

Cobb.—On April 15, 1955, at Lymington Hospital, Lymington, Hants, William Ernest Stanley Cobb, M.R.C.S., L.R.C.P.

Fisk.—On April 27, 1955, at Fairland House, Beccles, Suffolk, Harry Hope Fisk, M.R.C.S., L.R.C.P.

Hill.—On April 18, 1955, at the White House, Laverstock, Salisbury, Wilts, Horace Bryden Hill, M.B., B.S., M.R.C.P., Surgeon Captain, R.N., retired.

Hudson.—On May 17, 1955, at Watermillock House, Ullswater, Cumberland, James Hudson, M.D., formerly of Newcastle-upon-Tyne, aged 90.

King.—On April 15, 1955, at Carmarthen, Leslie Reginald King, M.B., B.Chir., late of Stow-on-the Wold, Glos.

Kingdon.—On April 2, 1955, at Trehunsey, Hillside Road, Sidmouth, Devon, Clement Thomas Cory Kingdon, M.D., aged 86.

Mitchell.—On April 28, 1955, at his home, Holmhurst, Greystones, Co. Wicklow, Robert Hollingsworth Mitchell, M.B., B.Ch., aged 51.

Patteson.—On April 19, 1955, Elizabeth Patteson, M.B., B.S., of 50, Weymouth Street, London, W.

Renner.—On April 28, 1955, in London, Edowo Awunor Penner, O.B.E., M.B., Ch.B., of Sierra Leone, West Africa, and Fintry House, Penn Road, Beaconsfield, Bucks, aged 61.

Trubridge.—On April 11, 1955, at his home, Lennox, Mass., U.S.A., Luigi Walter Trubridge, M.D.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Rapid Suppression of Lactation

Q.—*What is the best method of suppressing the milk, if an immediate cessation of breast-feeding is required?*

A.—If the decision against breast-feeding is already taken by the time delivery is complete, oestrogen therapy should be commenced immediately. Every hour counts and the sooner it is given after delivery the more effective it is. The aim is to give not less than 50 mg. stilboestrol (or 1.5 to 2 mg. ethinyl oestradiol) during the next four to seven days, and the dose should be high (say 5 mg. stilboestrol three times a day) during the first one or two days, and then gradually reduced. Bandaging of the breasts, aperients, and fluid restriction are unnecessary. Sometimes, at the end of the course of treatment, there is slight filling and secretion from the breasts, but this is not usually enough to require treatment. If it is, however, a supplementary modified and shortened course of oestrogen therapy can be given.

Once lactation is established it is much more difficult to suppress it with oestrogens. In such a situation a similar course of treatment is given in the hope that it will help. The breasts should be emptied at the commencement of treatment, but thereafter suckling, expression, the use of a breast pump, and any sort of local stimulation of the breasts are to be avoided.

Emotional Sweating

Q.—*Is there any treatment for excessive under-arm perspiration? My patient is a healthy young woman of 20 who has to change her clothing several times a day because of drenching sweats.*

A.—Though we know a good deal about sweat, the physiology of sweating, and the mechanism involved in disorders of sweating, it is unfortunately true that such knowledge is not readily translated into practical measures for the treatment of the suffering patient. Sweating may be a consequence of heat or of emotional disturbance, mental effort or sensory stimulation. Emotional sweating particularly affects the axillae, palms and soles, and forehead. The channel along which these disturbances act is nervous, and interruption of continuity of that channel at various levels may abolish the function of sweating.

Atropine, methanthelinium ("banthine"), and similar drugs are acetylcholine-inhibitors and so may protect the secretory mechanism from excessive stimulation, but they are usually effective only in doses so close to those producing untoward side-effects that they are not suitable for continuous use. They may with advantage be employed on particular occasions. Tincture of belladonna, 10–12 minims (0.6–1.2 ml.), may be taken half to one hour before the occasion and will usually be tolerated. In the last resort surgical interruption of the nervous channel by sympathectomy may be performed, usually with excellent results in the hands and feet but less successfully in the axillae. In a proportion of patients in whom the operation is performed in the upper sympathetic chain a more or less troublesome gustatory sweating of head or face has been reported as a sequel. It would be ideal if a similar blocking of impulse could be achieved by the use of those drugs which are known to be ganglion-blocking agents, such as the hexamethonium group. Unfortunately, as with the acetylcholine inhibitors, the effective dosage is so near the toxic dose that the continuous administration is dangerous. However, it may help to prescribe a tolerated dose of methylphenobarbitone, 3 gr. (200 mg.) twice daily, or amylobarbitone sodium, 1 gr. (65 mg.) thrice daily, which are the more effective of the barbiturates as ganglion-blocking agents.

While many patients suffer excessive sweating as a simple aberration of the normal physiology without any more significant psychological component than temperamental sensitiveness, a proportion are dependent upon psychological experience in childhood or adolescence, and such patients can with advantage be treated by the psychiatrist.

Routine treatment of patients with hyperidrosis is largely empirical and symptomatic and relies upon local measures. These are often not very successful. Most local measures depend in part upon a blocking of the gland orifice, and thus carry with them the risk of inflammatory and infective sequelae such as occur with any retained secretions. Others closely approach a direct irritant effect and have therefore to be used with caution. The patient should try a variety of remedies and in varying concentrations to discover which is most helpful and most acceptable. Bathing twice daily for ten minutes in a solution of bleaching powder, a teaspoonful to a quart (2.3 litres), increasing to a teaspoonful to a pint (0.6 litres), is helpful, care being taken to avoid producing a dermatitis. Formalin solution, aluminium acetate and chloride, each starting with a concentration of 1%, and 10% sodium hexametaphosphate, are other astringents of value. In some patients the use of the constant current (15 to 20 mA for 20 minutes twice a week) is effective, the negative pole being placed in the axilla. *X* rays (300 r at 90 kV through 2 mm. aluminium on three occasions at monthly intervals) should be prescribed only by those experienced and expert in this field and should not be repeated.

In conclusion, every patient with axillary hyperidrosis presents an individual medical problem, and should not be treated along routine or empirical lines until the medical and often the psychosomatic aspects have received attention.

Management of a Transverse Colostomy

Q.—*About three months ago a transverse colostomy was performed on a male patient aged 55 on account of a perforated diverticulum. Can you assist me towards (a) reducing the number of "actions" of the colostomy; and (b) increasing the solidity of the faeces? The patient has been instructed about diet and fluid restriction and takes "isogel" water-absorbing granules.*

A.—The "control" of a transverse colostomy can never be as good as that of an iliac operation. Since in this case the operation was done for a perforated diverticulum there is a possibility that the colostomy may later on be closed, but not, of course, until careful radiological studies of the distal bowel have shown its condition and patency. It is true, too, that all colostomies tend to settle down and become more manageable with the passage of time.

So far as diet is concerned each patient is a law unto himself; it requires painstaking observation on the part of the patient to find out the reaction of his bowel to various foods. It is usually thought best to give a comparatively non-residue-forming diet so that there is little bulk left to stimulate the colon, and, of course, as has been done already in this case, to keep the fluid intake down to a minimum. Kaolin is probably the most reliable material to make the bowel contents more solid and might be used instead of the "isogel." Green vegetables, onions, and so on tend to give a malodorous flatus and so should be avoided; activated charcoal in the form of biscuits is useful here. Habit-forming drugs to help control would naturally be used with great caution, but in the early stages of colostomy life the administration of a small dose of chlorodyne with meals is sometimes of help. In the case of a transverse colostomy, washing out the bowel is rarely of help and may even stimulate the bowel to greater activity.

Sobering Up with Aspirin

Q.—*What effect might 50 gr. (3.3 g.) of aspirin have on the clinical signs and symptoms of alcoholic intoxication, and on the alcohol content of the urine? Locally, the "boys" when out on a drinking round commonly use aspirin, as well as amphetamine and "oblivon," to help them sober up.*

A.—Individuals vary greatly in their sensitivity to aspirin. A dose of 50 gr. (3.3 g.) might produce nausea and vomiting in an average individual, and in a hypersensitive person might also give rise to tinnitus and deafness. It would not alter the signs or symptoms in a person who had been drinking nor make him appear to be more sober than if he had not taken it. The concentration of alcohol in the urine would not be affected by aspirin, and a knowledge of this figure or of the amount of alcohol consumed could be used as evidence in the usual way. Salicylates tend to interfere with the Cavett method for the assay of alcohol in urine, but accurate results are given by the Kozelka and Hine method. The "boys" would be well advised not to use "oblivon" (methylpentynol) as a means of sobering up, since its effects resemble those of alcohol and its use would tend to increase their apparent degree of intoxication. Aspirin would have no effect except through psychological mechanisms. Amphetamine taken after a patient has ceased to drink has a distinct sobering effect, and, taken the morning after, prevents or abates the usual symptoms of hangover.

Brown Tongue

Q.—*A man aged 39 complains of a foul taste in his mouth and a brown patch on his tongue for two years. On two occasions during that time the patch disappeared completely without treatment, and with it the foul taste. On examination four weeks ago there was an ulcer about one inch (2.5 cm.) long down the middle of the tongue at the junction of the anterior two-thirds and posterior third of the tongue. In and around it was a friable brown material removable by scraping. A barium swallow and meal showed no abnormality, but a swab gave a pure growth of a fungus of the genus Candida on culture. I treated him with tyrothricin lozenges for a week, which produced no improvement, so I followed this with 1% aqueous gentian violet as a paint night and morning for two weeks. This has resulted in amelioration of the foul taste, but the brown patch is still present on the anterior two-thirds to a slight extent, while the posterior one-third remains unchanged, for the patient cannot paint that without gagging. I should be grateful for advice on further treatment.*

A.—The brown patch may well be caused by infection with *Candida*, but it should be remembered that this yeast may be present only as a secondary invader or even as a harmless saprophyte. The ulceration suggests that there is an active infection, and the improvement with gentian violet would support the view that *Candida* is playing a pathogenic role. Tyrothricin has some fungicidal activity, so that improvement could occur, but one would expect more benefit from gentian violet.

Spontaneous change in the flora of the mouth is quite common in the healthy mouth. Van Leeuwenhoek, in his pioneer studies with the microscope, observed changes in his own buccal micro-flora after drinking hot coffee. It is not surprising, therefore, to find that spontaneous recovery from brown tongue occurs.

The foul taste is probably the result of some change in the enzymes in and near the taste buds, rather than the production of an evil-tasting substance by the invading organism. Why this is not a more frequent accompaniment of brown tongue has not been explained.

Treatment should be carried out by the doctor, and the posterior part of the tongue should be painted with gentian violet. If this is not successful it might be worth trying with 33% trichloracetic acid. Superficial *x*-ray treatment to the posterior part of the tongue is difficult and may be impossible, so that local application will have to be persisted in; it would be worth giving the patient a lozenge containing benzocaine or other local analgesic to suck before attempting to paint the remaining brown areas.

Right of Disposal of Wife's Dead Body

Q.—*In the case of a wife's death, who has the right of disposal of the body? Does a son or a daughter take precedence over the husband? Is the position in Scots law the same as in English law? If not, please indicate the difference.*

A.—In England, if a wife leaves a will, her executors (whoever they may be) have a statutory responsibility for her burial and they have the right of disposal of her dead body to the exclusion of her husband and family. If she leaves no will, her husband will be the next of kin, and the duty of burial and its complementary right of disposal rest on him.

In Scotland the English statutes do not apply and there is no reported decision of the courts on the subject: in consequence the position is far from clear. The best opinion appears to be that the husband's wishes would take precedence over those of the family of the deceased.

Lack of Beard

Q.—*A 33-year-old man is worried by his lack of beard. Each morning he shaves, but the soft texture of his beard and the sparsity of its distribution are a source of embarrassment to him. On examination he is well built. He has normal distribution of body hair with male configuration. He leads a normal sex life. The genital organs appear normal, if slightly below average size. What is the reason for the lack of beard? What is the possible treatment?*

A.—Normally the growth of the beard is dependent on a sufficiency of testosterone produced by the testicular interstitial tissue. Since, however, this man's sexual life and growth of body hair are normal, his lack of beard is unlikely to be due to deficiency of androgens. His condition is probably what is termed "resistance of the target organ"—that is, insensitivity of the hair follicles to androgenic stimulation. In such a case treatment will probably be ineffective, but a trial might be made of the daily local inunction of testosterone cream.

Some Problems of an Adolescent Girl

Q.—*I should be grateful for advice on the treatment of a healthy girl of 17, whose peripheral circulation is very poor. She has chilblains in winter, but her main complaint is the purplish discoloration of her legs and cheeks, worse in winter but never completely absent. There is also adolescent acne, a very coarse skin over the buttocks and outer surface of the arms, and a rather sour body odour in spite of daily baths and strict attention to hygiene.*

A.—A perniotic type of circulation with erythrocyanosis of the calves is a constitutional condition (unless acquired after acute poliomyelitis). It is often congenital, sometimes inherited, and is not very amenable to treatment. Small doses of thyroid extract (e.g., ¼ gr.—16 mg.—daily) are sometimes useful. The body must be kept warm to lessen peripheral vascular tone, and sudden considerable changes of temperature should be avoided. Central heating is a help, and on going out in cold weather warm clothing is essential. It is difficult to get a girl of 17 to wear woollen stockings, but she might be persuaded to put them on over nylons when she goes out of doors. Otherwise jeans should be worn. Elastic stockings are helpful because they are warm, and because they lessen the chronic oedema so often present with erythrocyanotic legs.

The other complaints are associated with adolescence, and time will effect a cure. Acne vulgaris can usually be improved by simple measures. The greasiness of the skin

requires the frequent use of soap and water or rinsing with weak cetrimide solution (½–1%). No grease should be applied to the skin, and if make-up is used a "liquid powder" is best. Chocolate and fried food must be avoided and the intake of starch reduced. Precipitated sulphur (6%) in calamine lotion may be applied at night. Fractional doses of *x* rays are helpful.

Watercress Cultivation

Q.—*I would be grateful if you can tell me whether any standards for the purity of water used for commercial watercress beds have ever been formulated. Is there any literature on the subject to which I could refer?*

A.—The Ministry of Agriculture and Fisheries has had two schemes governing the grade and designation of watercress. Under the National Mark Scheme certain physical qualities were demanded, but there was no mention made about water purity. In a trial scheme, first suggested in 1950, the same physical qualities were mentioned and extended to include a declaration that the ingoing water to the cress beds should be of drinking-water quality. Neither the National Mark Scheme (suspended at the beginning of the second world war) nor the trial scheme is at present in operation. The inquirer should refer to a paper[1] read before the Royal Sanitary Institute's Health Congress at Scarborough in 1954, which is an excellent review of information concerned with the hygiene of watercress cultivation.

The best policy to aim at would be to insist on a standard of purity for the water similar to the prevailing standard for rural water supplies, but in any case, as watercress is eaten in the fresh state, its consumption is somewhat hazardous, because it may be exposed to contamination from sources other than the water supply in which it is grown.[2] It is recommended by some authorities that watercress should be cleansed by soaking in a chlorine solution (free chlorine 150 parts per million) for about 10 minutes and then washed thoroughly in mains tap water. There is no wilting of the leaves and no appreciable taste after this procedure.

REFERENCES
1 *J. roy. Sanit. Inst.*, 1954, **74**, 875.
2 *Monthly Bull. Minist. Hlth (Lond.)*, 1953, **12**, 224.

Drug Treatment of Ménière's Disease

Q.—*What place have vasodilators, antihistamine drugs, vitamins, and streptomycin in the treatment of Ménière's disease? How successful are they? Are there any measures that will improve the hearing loss when the degree of loss does not appear to be static?*

A.—The morbid anatomical basis of Ménière's disease of the labyrinth consists in a dilatation of the endolymphatic system resulting from some disturbance in the circulation of the endolymph. The cause of this disturbance is as yet unknown. The beneficial effects of histamine and nicotinic acid described by Shelden and Horton[1] and Miles Atkinson[2–6] are likely to be dependent upon some improvement in the circulation of the endolymph, brought about by vasodilatation within the labyrinth. The good effects of cervical sympathectomy, described by Garnett Passe,[7] are likely to be brought about in the same way. The therapeutic effect of certain antihistamines—for example, dimenhydrinate, mepyramine, and promethazine—is probably dependent, like that of phenobarbitone, upon its depressant action upon the vestibular centres. Vitamin therapy has been recommended by a number of authors, in particular with vitamins A and B. The good results claimed have not been substantiated. Streptomycin has also been prescribed for Ménière's disease in view of its destructive effect upon the vestibular neurones. The use of streptomycin has, however, certain serious disadvantages. There is evidence that in addition to its effect upon the vestibular neurones it also brings about widespread pathological changes in the vestibulo-cerebellar pathways. The effect of this is a persistent state of general imbalance which in elderly people may be very serious.

Improvement of hearing sometimes follows vasodilator therapy—for example, intravenous infusion of histamine. It must, however, be added that similar improvements in hearing sometimes appear to occur spontaneously in the natural course of the disease.

REFERENCES
1 *Proc. Mayo Clin.*, 1940, **15**, 17.
2 *Arch. Otolaryng. (Chicago)*, 1944, **40**, 101.
3 *J. Amer. med. Ass.*, 1941, **116**, 1753.
4 Ibid., 1942, **119**, 4.
5 *Arch. Otolaryng. (Chicago)*, 1943, **37**, 40.
6 *Eye, Ear, Nose, Thr. Monthly*, 1944, **23**, 436.
7 *Arch. Otolaryng. (Chicago)*, 1953, **57**, 257.

Irritation of Tip of Penis

Q.—*I have a patient aged 76 years who complains of intense irritation of the tip of the penis. The irritation is apt to come on at any time of the day or night, and is extremely embarrassing, as the desire to scratch is almost unendurable. I would welcome some suggestions on diagnosis and treatment.*

A.—I assume that the urine has been tested for sugar, and that there is no urethritis or balanitis to account for the irritation. Also that the meatus appears normal and that there are no disturbances of micturition such as difficulty, frequency, or pain. If nothing can be found to account for the meatal irritation, I should give the patient a course of testosterone intramuscularly on the supposition that it is due to senile tissue changes. Testosterone is often very effective in the treatment of senile pruritus. It might also be worth while giving the patient some 1% cinchocaine ointment for local use.

Ritual Circumcision

Q.—*My son, now aged 2 years, had a ritual circumcision performed when he was 7 days old. I was very worried at the time, as there was practically no penile skin left, but I was assured that this was quite in order. As a matter of fact the wound healed quite well, and we have had no trouble: the shaft of the penis is almost completely covered by good scar tissue and there remains a small area of normal skin at the root. Is this in fact in accordance with the established principles of ritual circumcision, and will the scar tissue give rise to any trouble in future years?*

A.—To remove so much skin is certainly not in accordance with ritual ceremony, and it is fortunate that the wound healed so well. The skin of the penis is very elastic, and it is quite easy for a priest (or medical man) to pull down too much at the time of circumcision. But the scar should not cause trouble in future years.

Corrections.—The late Dr. John Lowe did much research on the treatment of leprosy by sulphones, not sulphonamides as inadvertently stated in Sir Arthur MacNalty's appreciation (May 21, p. 1283).

In announcing a research grant to Dr. Hilda Roberts (May 28, p. 1351) we described her present appointment as lecturer in anaesthesia in the Postgraduate Medical School. Dr. Roberts resigned from that post on March 31 and is now an honorary research assistant of the Institute of Obstetrics and Gynaecology at Hammersmith Hospital.

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